



รายงานวิจัยฉบับสมบูรณ์

โครงการ: การวิจัยเชิงสังเคราะห์และการวิจัยนิพนธ์ต้นฉบับ
เพื่อแก้ไขปัญหาสุขภาพที่สำคัญในภาค
ตะวันออกเฉียงเหนือของประเทศไทย

โดย ศ.น.พ.ภิเศก ลุมพิกานนท์

พฤศจิกายน 2560

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ผู้วิจัย ศ.น.พ.ภิเศก ลุ่มพิกานนท์
ภาควิชาสถิติศาสตร์และนรีเวชวิทยา
คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น

สนับสนุนโดยสำนักงานกองทุนสนับสนุนการวิจัย
และมหาวิทยาลัยขอนแก่น

กิตติกรรมประกาศ

ขอขอบคุณสำนักงานกองทุนสนับสนุนการวิจัย สกว. และมหาวิทยาลัยขอนแก่น ที่ให้งบประมาณสนับสนุนโครงการศาสตราจารย์วิจัยดีเด่น ของศาสตราจารย์นายแพทย์ภิเศก ลุมพิกานนท์ ขอขอบคุณฝ่ายวิชาการ สำนักงานกองทุนสนับสนุนการวิจัย ที่อำนวยความสะดวกในการดำเนินงานของโครงการ ขอขอบคุณผู้ร่วมวิจัย ผู้ร่วมเครือข่ายงานวิจัยทุกท่านที่ร่วมแรงร่วมใจทำงานวิจัยจนสำเร็จลุล่วงไปได้ด้วยดี และขอขอบคุณนางสาวระเบียบ ภูมิบ้านค้อ ผู้ดูแลงานธุรการของโครงการอย่างมีประสิทธิภาพ

ศาสตราจารย์นายแพทย์ภิเศก ลุมพิกานนท์

บทคัดย่อ

รหัสโครงการ: DPG5780003

ชื่อโครงการ: การวิจัยเชิงสังเคราะห์และการวิจัยนิพนธ์ต้นฉบับเพื่อแก้ไขปัญหาสุขภาพที่สำคัญ
ในภาคตะวันออกเฉียงเหนือของประเทศไทย

ชื่อหลักวิจัย: ศาสตราจารย์นายแพทย์ภิเศก ลุมพิกานนท์

สถาบัน: ภาควิชาสูติศาสตร์และนรีเวชวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น

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ระยะเวลาโครงการ: 3 ปี (17 มีนาคม 2557 ถึง 18 มีนาคม 2560)

โครงการนี้มีวัตถุประสงค์ที่จะทำการวิจัยเชิงสังเคราะห์ (systematic review and meta-analysis) และงานวิจัยนิพนธ์ต้นฉบับถ้ามีความเหมาะสม เพื่อแก้ปัญหาอนามัยเจริญพันธุ์และอื่นๆ และทำการวิจัยปัญหาสุขภาพมารดาและทารกปริกำเนิดโดยใช้ฐานข้อมูล Multi-country survey ขององค์การอนามัยโลก รวมทั้งการสร้างนักวิจัยรุ่นใหม่เพื่อสร้างเครือข่ายที่จะทำวิจัยร่วมกันในอนาคต

ในช่วงระยะเวลา 3 ปีครึ่ง (ข้อตกลงเดิม 3 ปี และขยายเวลาอีก 6 เดือน) ทางโครงการได้ตีพิมพ์ Cochrane reviews 18 ฉบับ และ Cochrane protocols 6 ฉบับ (ซึ่งกำลังดำเนินการให้เป็น Cochrane review) ใน วารสาร Cochrane Library (Impact factor 2016 = 6.124) สำหรับงานวิจัยนิพนธ์ต้นฉบับเราได้ตีพิมพ์ 2 ฉบับ และกำลังจัดทำ manuscripts อยู่อีก 4 ฉบับ ในช่วงระยะเวลาเดียวกันนี้เรายังมีการทำวิจัยอื่น ๆ ที่ไม่ได้ใช้งบประมาณของสกว. และได้ตีพิมพ์ 15 ฉบับ ใน international peer reviewed journals

งาน Cochrane reviews ของเราได้มีการนำไปอ้างอิงใน international peer reviewed journals 180 ครั้ง และงาน Cochrane reviews 7 ฉบับ ของเราได้ถูกนำไปเป็นเอกสารอ้างอิงใน Guidelines 3 ฉบับ ขององค์การอนามัยโลก

ปัจจุบันเครือข่ายของเรามีสมาชิก 36 คน จาก 8 สถาบัน ในจำนวนนี้เป็นนักวิจัยหน้าใหม่จำนวน 18 คน มีการจัดประชุมวิชาการประจำปี 2 ครั้ง จัด Workshop เรื่อง Cochrane Protocol Development 10 ครั้ง ให้มหาวิทยาลัยขอนแก่น กรมการแพทย์และกรมควบคุมโรค กระทรวงสาธารณสุข ราชวิทยาลัยสูตินรีแพทย์แห่งประเทศไทย สำนักแพทยศาสตร์มหาวิทยาลัยสารคาม และ Hue University of Medicine and Pharmacy, Vietnam

ยังมีโครงการวิจัยนิพนธ์ต้นฉบับจำนวน 3 เรื่อง ที่กำลังดำเนินการอยู่ซึ่งคาดว่าจะเก็บข้อมูลได้เรียบร้อยใน 6 เดือนข้างหน้า

Keywords: Research synthesis, systematic review, Cochrane, original research,
Research collaboration, health problems

Abstract

Project Code: DPG5780003

Project Title: Research synthesis and original research to address major health problems in Northeast Thailand

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Project Period: 3 years

This project aimed at addressing reproductive and other health problems by conducting research synthesis (systematic review and meta-analysis) and original (mainly collaborative) studies as appropriated and to do secondary analysis addressing maternal and perinatal health issues using the existing WHO multi-country survey. It also wanted to build new researchers as well as to form a network of researchers to conduct more research together in the future.

During the three and a half year period (3 year original contract + 6 month extension) we have published 18 Cochrane reviews and 6 Cochrane protocols in Cochrane Library (Impact factor 2016 = 6.124). We also published 2 papers in international peer reviewed journals and working on 4 manuscripts. In this period we also involved in other research activities (not financially supported by TRF) and published 15 more papers in international peer reviewed journals.

Our Cochrane reviews were cited 180 times in international peer reviewed journals. Eight of our published Cochrane reviews were used as references in 3 World Health Organization Guidelines.

We are currently working with 36 researchers from 8 institutes, among these there are 18 new researchers. We have organized 2 annual scientific conferences and conducting 10 Cochrane protocol development workshops for Khon Kaen University, Departments of Medical Services and Disease Prevention, Ministry of Public Health, Royal Thai College of Obstetricians and Gynaecologists, Faculty of Medicine, Maha Sarakham University and Hue University of Medicine and Pharmacy, Vietnam.

There are 3 ongoing multicenter collaborative studies that are hopefully to be finished in the next 6 months.

Keywords: Research synthesis, systematic review, Cochrane, original research,
Research collaboration, health problems

Executive Summary

1. ความสำคัญที่มาของปัญหา

Reproductive and perinatal healths are important areas that require more research to address. Important issues include low birth weight, maternal mortality and morbidity, postpartum hemorrhage, birth asphyxia, etc. Recently, we have been collaborating in a multi-country survey with the Department of Reproductive Health and Research of the World Health Organization to address severe maternal outcomes (maternal mortality and maternal near miss). This initiative collected data from more than 300,000 mothers and their newborns. The protocol and the main paper of this project were published elsewhere. This data set can be used for secondary analyses addressing various maternal and neonatal health issues. There are many major health issues that are quite specific or endemic for northeast Thailand. These include opisthorchiasis and cholangiocarcinoma, iodine deficiency, thalassemia, mental disorders, etc. The incidence of cholangiocarcinoma in northeast Thailand is highest in the world. Currently, there are no practical and sensitive methods for early detection of cholangiocarcinoma. There are still controversies about appropriate surgical interventions for patients with cholangiocarcinoma. Knowledge about appropriate chemotherapy for patients with cholangiocarcinoma is also very limited.

Iodine deficiency is a long standing major health problem especially in northeast Thailand. Although severe forms of iodine deficiency such as goiter or mental retardation are quite rare, there are still other important consequences of iodine deficiency including lowering of intelligence quotient (IQ), short attention disorder, learning disability and less quality population. Ministry of Public Health together with some other organizations has been trying to address this very important problem. However, in northeast Thailand according to the most recent survey by the department of health, the prevalence of iodine deficiency in pregnant women is still the highest in the country (unofficial report) and perhaps one of the highest in the world. This correlates very well with the recent survey by the department of mental diseases which indicates that the average IQ of children in most of the provinces in northeast Thailand are lower compared to other regions (unofficial report). This is also a very important preventable health problem that needs to be solved as soon as possible.

There are also many other important health problems affecting people in northeast Thailand. These include thalassemia, diabetes mellitus; mental disorders especially depression, eye diseases, etc.

Evidence based healthcare and lifelong learning are very important principles in taking effective care of patients. Interventions for patient care should be based on up to date and reliable research evidences rather than personal opinion or common practices. Research synthesis (systematic review and meta-analysis) is now generally accepted as the best research design in evaluating the effectiveness of healthcare interventions. The Cochrane Collaboration is an international network of more than 31,000 dedicated people from over 120 countries. It aims at helping healthcare practitioners, policy-makers, patients, etc. to make well-informed decisions about health care, by preparing, updating, and promoting the accessibility of Cochrane Reviews. Currently, over 5,000 Cochrane Reviews are published online in the *Cochrane Database of Systematic Reviews*, part of *The Cochrane Library*. The contents of Cochrane Reviews published in the Cochrane Library are updated regularly. The latest (2016) impact factor of the Cochrane Library was 6.124, ranking number 11th among biomedical journals. The Thai Cochrane Network which is a branch of the Australasian Cochrane Centre is based at Faculty of Medicine, Khon Kaen University. Pisake Lumbiganon was the founder and the current coordinator of this Thai Cochrane Network.

We aim at conducting Cochrane reviews addressing major health problems in northeast Thailand as indicated above. Original research will be conducted as necessary and feasible.

2. วัตถุประสงค์

- 2.1 To conduct systematic reviews evaluating interventions and diagnostic test accuracy for major health problems especially for northeast Thailand.
- 2.2 To conduct original research when necessary and feasible based on the results of systematic reviews.
- 2.3 To do secondary analysis addressing maternal and perinatal health issues using the existing WHO multi-country survey.

3. ระเบียบวิธีวิจัยโดยสรุป

- 3.1 Research synthesis (systematic review and meta-analysis) following Cochrane Methodology.
- 3.2 Original research as appropriated based on the results of Cochrane reviews.
- 3.3 Secondary analyses of the WHO multi-country survey data.
- 3.4 Workshops for training researchers to increase their competency

4. แผนการดำเนินงานวิจัยในแต่ละช่วง 6 เดือน ตลอดระยะเวลาในโครงการ

Period	Expected papers published in impact factor journals	New authors recruited	Having new projects
1 st 6 months	2 papers	1-3 persons	1-3 projects
2 nd 6 months	3-5 papers	1-3 persons	1-3 projects
3 rd 6 months	3-5 papers	1-3 persons	1-3 projects
4 th 6 months	3-5 papers	1-3 persons	1-3 projects
5 th 6 months	3-5 papers	1- 3 persons	1-3 projects
last 6 months	3-5 papers	1- 3 persons	1-3 projects
Total	17-25 papers	6-18 persons	6-18 projects

5. ผลที่คาดว่าจะได้จากโครงการ (output, outcome และ impact)

5.1 ผลงานตีพิมพ์ในวารสารวิชาการนานาชาติ โดยระบุชื่อเรื่องและชื่อวารสารวิชาการระดับนานาชาติที่คาดว่าจะลงตีพิมพ์ พร้อมค่า impact factor

Potential international peer review journals for submitting publications:

- 5.1.1 Cochrane Database of Systematic Review (5.785)
- 5.1.2 British Journal of Obstetrics & Gynaecology (3.76)
- 5.1.3 International Journal of Obstetrics and Gynecology (1.836)
- 5.1.4 Journal of Obstetrics and Gynecology Research (0.841)
- 5.1.5 Bulletin of the World Health Organization (5.25)
- 5.1.6 BMC Cancer (3.33)
- 5.1.7 BMC Pregnancy and Childbirth (2.08)
- 5.1.8 BMC Public Health (2.08)
- 5.1.9 BMC Complementary and Alternative Medicine (2.08)
- 5.1.10 BMC Women's Health (1.51)
- 5.1.11 BMC Health Service Research (1.77)
- 5.1.12 BMC Medical Research Methodology (2.21)
- 5.1.13 Reproductive Health (1.31)

5.2 ผลงานการจดสิทธิบัตร โดยคาดซื้อเรื่องที่จะจดสิทธิบัตร
ไม่มี

5.3 หนังสือ
ไม่มี

5.4 จำนวนนักวิจัยที่สร้างจากโครงการ

- จำนวนนักวิจัยระดับหลังปริญญาเอก : จำนวน 10 - 15 คน
- จำนวนนักวิจัยระดับปริญญาเอก : -
- จำนวนนักศึกษาระดับปริญญาโท : จำนวน 10 คน

5.5 ประโยชน์ที่คาดว่าจะได้รับ และคาดการณ์ผลการวิจัยไปใช้ประโยชน์เชิงพาณิชย์
เชิงสาธารณะหรือเชิงนโยบาย

5.5.1 Increasing number of competent researchers for both systematic reviews
and original research.

5.5.2 Publication of 17-25 papers in high impact factor journals addressing major
health issues in northeast Thailand.

5.5.3 Strengthening the Thai Cochrane Network to become reference center for
Laos PDR, Vietnam, Cambodia and Myanmar.

5.5.4 Strengthening the role of Khon Kaen University as a research university

5.5.5 Knowledge to solve health problems in northeast Thailand

5.6 ผลกระทบต่อสังคมในวงกว้าง

- ประชาชนในภาคตะวันออกเฉียงเหนือและของประเทศมีสุขภาพดีขึ้น

เนื้อหางานวิจัย

1. **Systematic reviews evaluating interventions and diagnostic test accuracy for major health problems especially for northeast Thailand.** มีผลงาน **Cochrane reviews** จำนวน 18 ฉบับ และ **Cochrane Protocol** จำนวน 6 ฉบับ ดังต่อไปนี้ (รายละเอียดดูในภาคผนวกที่ 1)

Cochrane reviews:

- 1.1 **Chawanpaiboon S, Laopaiboon M, Lumbiganon P, Sangkomkarn US, Dowswell T.** Terbutaline pump maintenance therapy after threatened preterm labour for reducing adverse neonatal outcomes. *Cochrane Database Syst Rev.* 2014, Issue 3. Art. No.: CD010800.
- 1.2 **Lumbiganon P, Thinkhamrop J, Thinkhamrop B, Tolosa JE.** Vaginal chlorhexidine during labour for preventing maternal and neonatal infections (excluding Group B Streptococcal and HIV). *Cochrane Database Syst Rev* 2014, Issue 9. Art. No.: CD004070.
- 1.3 **Siriwachirachai T, Sangkomkarn US, Lumbiganon P, Laopaiboon M.** Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections. *Cochrane Database Syst Rev* 2014, Issue 11:CD007772.
- 1.4 **Sangkomkarn US, Lumbiganon P, Laopaiboon M.** Hepatitis B vaccination during pregnancy for preventing infant infection. *Cochrane Database Syst Rev* 2014, Issue 11:CD007879.
- 1.5 **Tangjitgamol S, Katanyoo K, Laopaiboon M, Lumbiganon P, Manusirivithaya S, Supawattanabodee B.** Adjuvant chemotherapy after concurrent chemoradiation for locally advanced cervical cancer. *Cochrane Database Syst Rev* 2014, Issue 12:CD010401.
- 1.6 **Chaithongwongwatthana S, Yamasmit W, Limpongsanurak S, Lumbiganon P, Tolosa JE.** Pneumococcal vaccination during pregnancy for preventing infant infection. *Cochrane Database Syst Rev* 2015, Issue 1. Art. No.:CD004903.
- 1.7 **Buppasiri P, Lumbiganon P, Thinkhamrop J, Ngamjarus C, Laopaiboon M, Medley N.** Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes. *Cochrane Database Syst Rev* 2015, Issue 2. Art. No.:CD007079.

- 1.8 **Sangkomkamhang US, Lumbiganon P**, Prasertcharoensuk W, **Laopaiboon M**. Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery. Cochrane Database Syst Rev 2015, Issue 2. Art. No.:CD006178.
- 1.9 **Thinkhamrop J**, Hofmeyr GJ, Adetoro O, **Lumbiganon P**, Ota E. Antibiotic prophylaxis during the second and third trimester to reduce adverse pregnancy outcomes and morbidity. Cochrane Database of Systematic Reviews 2015, Issue 6. Art. No.: CD002250.
- 1.10 **Muktabhant B**, Lawrie TA, **Lumbiganon P**, **Laopaiboon M**. Diet or exercise, or both, for preventing excessive weight gain in pregnancy. Cochrane Database of Systematic Reviews 2015, Issue 6. Art. No.: CD007145.
- 1.11 **Rungsiprakarn P, Laopaiboon M, Sangkomkamhang US, Lumbiganon P**, Pratt JJ. Interventions for treating constipation in pregnancy. Cochrane Database of Systematic Reviews 2015, Issue 9. Art. No.: CD011448.
- 1.12 **Tangjitgamol S**, Manusirivithaya S, **Laopaiboon M, Lumbiganon P**, Bryant A. Interval debulking surgery for advanced epithelial ovarian cancer. Cochrane Database of Systematic Reviews 2016, Issue 1. Art. No.: CD006014.
- 1.13 **Rungsiprakarn P, Laopaiboon M, Sangkomkamhang US, Lumbiganon P**. Pharmacological interventions for generalised itching (not caused by systemic disease or skin lesions) in pregnancy. Cochrane Database of Systematic Reviews 2016 Issue 2. Art. No.:CD011351.
- 1.14 **Kietpeerakool C, Supoken A, Laopaiboon M, Lumbiganon P**. Effectiveness of tranexamic acid in reducing blood loss during cytoreductive surgery for advanced ovarian cancer. Cochrane Database of Systematic Reviews 2016, Issue 1. Art. No.: CD011732.
- 1.15 **Lumbiganon P**, Martis R, **Laopaiboon M**, Festin MR, Ho JJ, Hakimi M. Antenatal breastfeeding education for increasing breastfeeding duration. Cochrane Database of Systematic Reviews 2016, Issue 12. Art. No.: CD006425.
- 1.16 **Luong Thanh BY, Laopaiboon M**, Koh D, Sakunkoo P, **Moe H**. Behavioural interventions to promote workers' use of respiratory protective equipment. Cochrane Database of Systematic Reviews 2016, Issue 12. Art. No.: CD010157.

- 1.17 **Kietpeerakool C**, Chumworathayi B, **Thinkhamrop J**, Ussahgij B, **Lumbiganon P**. Antibiotics for infection prevention after excision of the cervical transformation zone. Cochrane Database of Systematic Reviews 2017, Issue 1. Art. No.: CD009957.
- 1.18 **Sothornwit J**, **Werawatakul Y**, **Kaewrudee S**, **Lumbiganon P**, **Laopaiboon M**. Immediate versus delayed postpartum insertion of contraceptive implant for contraception. Cochrane Database Syst Rev 2017, Issue 4. Art. No.:CD011913

Cochrane Protocol:

- 1.19 **Lumbiganon P**, **Werawatakul Y**, **Laopaiboon M**, **Sothornwit J**. Interventions for intra-operative pain relief during postpartum mini-laparotomy tubal ligation. Cochrane Database of Systematic Reviews 2015, Issue 7. Art. No.: CD011807.
- 1.20 **Thamronganantasakul K**, Supakalin N, **Kietpeerakool C**, **Pattanittum P**, **Lumbiganon P**. Extended-field irradiation for locally advanced cervical cancer. Cochrane Database of Systematic Reviews 2016, Issue 7. Art. No.: CD012301.
- 1.21 **Supoken A**, **Kietpeerakool C**, **Laopaiboon M**, **Lumbiganon P**. Simple versus radical hysterectomy with pelvic lymphadenectomy for women with stage IA2-IB1 cervical cancer. Cochrane Database of Systematic Reviews 2016, Issue 8. Art. No.: CD012335.
- 1.22 **Temtanakitpaisan T**, **Buppasiri P**, **Chongsomchai C**, **Kietpeerakool C**, **Lumbiganon P**, **Laopaiboon M**. Antibiotics for the prevention of infection after continence surgery in women with stress urinary incontinence. Cochrane Database of Systematic Reviews 2016, Issue 12. Art. No.: CD012457.
- 1.23 **Luvira V**, Satitkarnmanee E, Pugkhem A, **Kietpeerakool C**, **Lumbiganon P**, Kamsa-ard S, **Pattanittum P**. Postoperative adjuvant chemotherapy for resectable cholangiocarcinoma. Cochrane Database of Systematic Reviews 2017, Issue 9. Art. No.: CD012814.
- 1.24 **Kietpeerakool C**, **Aue-aungkul A**, Galaal K, Ngamjarus C, **Lumbiganon P**. Nerve-sparing radical hysterectomy compared to standard radical hysterectomy for women with early stage cervical cancer (stage Ia2 to IIa). Cochrane Database of Systematic Reviews 2017, Issue 10. Art. No.: CD012828.

2. Original research ได้ตีพิมพ์งานวิจัยไปแล้ว 2 ฉบับ (รายละเอียดดูในภาคผนวกที่ 2)

- 2.1 Luexay P, **Malinee L, Pisake L**, Marie-Hélène BC. Maternal near-miss and mortality in Sayaboury Province, Lao PDR. BMC Public Health. 2014 Sep 12; 14: 945.
- 2.2 Kankoon N, **Lumbiganon P, Kietpeerakool C, Sangkomkamhang U**, Betrán AP, Robson M. Cesarean rates and severe maternal and neonatal outcomes according to the Robson 10-Group Classification System in Khon Kaen Province, Thailand. Int J Gynaecol Obstet. 2017 Nov 2.

และกำลังดำเนินการเก็บข้อมูลอีก 3 เรื่อง ได้แก่

- 2.3 Restrictive versus Routine Episiotomy: A Randomized Controlled Trial
- 2.4 Depot Medroxyprogesterone Acetate (DMPA) and Endometrial Cancer: A multicenter case-control study
- 2.5 Multicenter study of the inadequate calcium consumption rate in Thai pregnant women

3. Secondary analysis addressing maternal and perinatal health issues using the existing WHO multi-country survey. ได้ตีพิมพ์ไปแล้วจำนวน 1 ฉบับ ได้แก่ (รายละเอียดดูในภาคผนวกที่ 3)

- 3.1 Mya KS, **Laopaiboon M**, Vogel JP, Cecatti JG, Souza JP, Gulmezoglu AM, Ortiz-Panoso E, Mittal S, **Lumbiganon P**; WHO multi-country survey on maternal and newborn health research network. Management of pregnancy at and beyond 41 completed weeks of gestation in low-risk women: a secondary analysis of two WHO multi-country surveys on maternal and newborn health. Reprod Health. 2017 Oct 30; 14(1): 141.

และกำลังดำเนินการวิเคราะห์ข้อมูลอยู่อีก 3 เรื่อง ได้แก่

- 3.2 Anaesthetic use during Caesarean delivery and maternal and neonatal outcomes
- 3.3 Mode of delivery and pregnancy outcomes in preterm birth
- 3.4 Pregnancy outcomes after repeated Caesarean Section

4. งานวิจัยอื่น ๆ ที่ได้ดำเนินการในระยะเวลาเดียวกันนี้โดยไม่ได้ใช้งบประมาณของ สกว. มีการตีพิมพ์จำนวน 15 ฉบับ ดังต่อไปนี้ (รายละเอียดดูในภาคผนวกที่ 4)

- 4.1 Meriardi M, Widmer M, Gülmezoglu AM, Abdel-Aleem H, Bega G, Benachi A, Carroli G, Cecatti JG, Diemert A, Gonzalez R, Hecher K, Jensen LN, Johnsen SL, Kiserud T, Kriplani A, **Lumbiganon P**, Tabor A, Talegawkar SA, Tshefu A, Wojdyla D, Platt L. WHO multicentre study for the development of growth standards from fetal life to childhood: the fetal component. BMC Pregnancy Childbirth. 2014 May 2; 14: 157.
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Outputs ที่ได้จากโครงการ (2557-2560)

1. Systematic reviews evaluating interventions and diagnostic test accuracy for major health problems especially for northeast Thailand. มีผลงาน Cochrane reviews จำนวน 18 ฉบับ และ Cochrane Protocol จำนวน 6 ฉบับ ดังต่อไปนี้ (รายละเอียดดูในภาคผนวกที่ 1)
2. Original research ได้ตีพิมพ์งานวิจัยไปแล้ว 2 ฉบับ (รายละเอียดดูในภาคผนวกที่ 2)
3. Secondary analysis addressing maternal and perinatal health issues using the existing WHO multi-country survey. ได้ตีพิมพ์ไปแล้วจำนวน 1 ฉบับ ได้แก่ (รายละเอียดดูในภาคผนวกที่ 3)
4. งานวิจัยอื่น ๆ ที่ได้ดำเนินการในระยะเวลาเดียวกันนี้โดยไม่ได้ใช้งบประมาณของสกว. มีการตีพิมพ์จำนวน 15 ฉบับ ดังต่อไปนี้ (รายละเอียดดูในภาคผนวกที่ 4)
5. มีนักวิจัยเข้าร่วมในโครงการจำนวน 36 คน จาก 8 สถาบัน (กรุณาดูรายละเอียดในภาคผนวกที่ 5)
6. ประเทศไทยมีโครงการวิจัยเชิงสังเคราะห์ที่ทำร่วมกับ Cochrane Collaboration และปัจจุบันเป็นอันดับที่ 6 ใน Asia รองจากจีน อินเดีย ญี่ปุ่น สิงคโปร์ และมาเลเซีย (กรุณาดูเอกสารในภาคผนวกที่ 6)
7. งานวิจัยที่ได้ตีพิมพ์ใน Cochrane Library ได้นำไปอ้างอิงในวารสารต่างประเทศ จำนวน 180 ครั้ง (กรุณาดูรายละเอียดในภาคผนวกที่ 7)
8. งานวิจัยที่ได้ตีพิมพ์ใน Cochrane Library จำนวน 7 ฉบับ ได้รับการนำไปอ้างอิงใน WHO Guidelines (กรุณาดูรายละเอียดในภาคผนวกที่ 8)



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Terbutaline pump maintenance therapy after threatened preterm labour for reducing adverse neonatal outcomes (Review)

Chawanpaiboon S, Laopaiboon M, Lumbiganon P, Sangkomkarn US, Dowswell T

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	2
OBJECTIVES	4
METHODS	4
RESULTS	8
Figure 1.	9
Figure 2.	11
Figure 3.	12
DISCUSSION	14
AUTHORS' CONCLUSIONS	15
ACKNOWLEDGEMENTS	16
REFERENCES	16
CHARACTERISTICS OF STUDIES	18
DATA AND ANALYSES	24
Analysis 1.1. Comparison 1 Terbutaline pump versus saline pump, Outcome 1 Respiratory distress syndrome.	25
Analysis 1.2. Comparison 1 Terbutaline pump versus saline pump, Outcome 2 Gestational age at birth (in weeks).	25
Analysis 1.3. Comparison 1 Terbutaline pump versus saline pump, Outcome 3 Very preterm birth (< 34 weeks).	26
Analysis 1.4. Comparison 1 Terbutaline pump versus saline pump, Outcome 4 Preterm birth (< 37 weeks).	27
Analysis 1.5. Comparison 1 Terbutaline pump versus saline pump, Outcome 5 Birthweight.	27
Analysis 1.6. Comparison 1 Terbutaline pump versus saline pump, Outcome 6 Neonatal intensive care unit admissions at > 24 hours.	28
Analysis 1.7. Comparison 1 Terbutaline pump versus saline pump, Outcome 7 Early discontinuation.	28
Analysis 2.1. Comparison 2 Terbutaline pump versus oral terbutaline, Outcome 1 Respiratory distress syndrome.	29
Analysis 2.2. Comparison 2 Terbutaline pump versus oral terbutaline, Outcome 2 Gestational age at birth (in weeks).	29
Analysis 2.3. Comparison 2 Terbutaline pump versus oral terbutaline, Outcome 3 Birthweight.	30
Analysis 2.4. Comparison 2 Terbutaline pump versus oral terbutaline, Outcome 4 Early discontinuation.	30
CONTRIBUTIONS OF AUTHORS	30
DECLARATIONS OF INTEREST	31
SOURCES OF SUPPORT	31
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	31
NOTES	31
INDEX TERMS	31

Terbutaline pump maintenance therapy after threatened preterm labour for reducing adverse neonatal outcomes

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ABSTRACT

Background

After successful inhibition of threatened preterm labour women are at high risk of recurrent preterm labour. Terbutaline pump maintenance therapy has been used to reduce adverse neonatal outcomes. This review replaces an earlier Cochrane review, published in 2002, which is no longer being updated by the team.

Objectives

To determine the effectiveness of terbutaline pump maintenance therapy after threatened preterm labour in reducing adverse neonatal outcomes.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 January 2014) and reference lists of retrieved studies.

Selection criteria

Randomised controlled trials comparing terbutaline pump therapy with alternative therapy, placebo, or no therapy after arrest of threatened preterm labour.

Data collection and analysis

Two review authors independently assessed the studies for inclusion and then extracted data as eligible for inclusion in qualitative and quantitative synthesis (meta-analysis).

Main results

Four studies were included with a total of 234 women randomised. The overall methodological quality of the included studies was mixed; two studies provided very little information on study methods, there was high sample attrition in one study and in three studies the risk of performance bias was high. We found no strong evidence that terbutaline maintenance therapy offered any advantages over saline placebo or oral terbutaline maintenance therapy in reducing adverse neonatal outcomes by prolonging pregnancy among women with arrested preterm labour. The mean difference (MD) for gestational age at birth was -0.14 weeks (95% confidence interval (CI) -1.66 to 1.38) for terbutaline pump therapy compared with saline placebo pump for two trials combined. One trial reported a risk ratio (RR) of 1.17 (95% CI 0.79 to 1.73) for preterm birth (less than 37 completed weeks) and a RR of 0.97 (95% CI 0.51 to 1.84) of very preterm birth (less than 34 completed weeks) for terbutaline pump compared with saline placebo pump. We found no evidence that terbutaline pump therapy was associated with statistically significant reductions in infant respiratory distress syndrome, or neonatal intensive care unit admission compared with placebo. Compared with oral terbutaline, we found no evidence that pump therapy increased the rate of therapy continuation, or reduced the rate of infant complications or maternal hospital re-admissions. One study suggested that pump therapy resulted in significantly increased weekly cost/woman, \$580 versus \$12.50 ($P < 0.01$). No data were reported on long-term infant outcomes.

Authors' conclusions

We found no evidence that terbutaline pump maintenance therapy decreased adverse neonatal outcomes. Taken together with the lack of evidence of benefit, its substantial expense and the lack of information on the safety of the therapy do not support its use in the management of arrested preterm labour. Future use should only be in the context of well-conducted, adequately powered randomised controlled trials.

PLAIN LANGUAGE SUMMARY

Terbutaline pump maintenance therapy after threatened preterm labour for reducing adverse neonatal outcomes

Babies born too early (preterm birth) are at high risk of poor outcomes, and the earlier they are born the greater their risk. Preterm babies are more likely to die or have serious disability as children, including cerebral palsy and other similar conditions. Women who go into very early labour (before 34 weeks) and have their contractions stopped by intravenous drugs are at high risk of going back into preterm labour. Terbutaline is a drug that can relax the uterus and possibly stop contractions. Taken orally, though, it does not seem to prevent contractions returning. Another option is to use a small portable pump that feeds a continuous dose of terbutaline under the skin. This has the advantage of using a lower daily dose with faster onset of action and good tolerability because of fewer side effects than when taken by mouth. We found four studies involving 234 women who had been in preterm labour and had their contractions stopped. We found no evidence of terbutaline maintenance therapy offering any advantages over saline placebo pump or oral terbutaline maintenance therapy in reducing adverse neonatal outcomes by prolonging pregnancy among women with arrested preterm labour. The review found there are not enough large trials to show whether terbutaline pump maintenance therapy is safe or effective.

BACKGROUND

Description of the condition

Preterm birth refers to a birth that occurs before 37 completed weeks of gestation. About 40% of preterm births are due to complications mandating early delivery such as placenta previa, pre-

eclampsia, fetal growth restriction and infection. Approximately 30% of preterm births occur following preterm pre-labour rupture of membranes (PPROM) and the remainder are due to spontaneous preterm labour ([Beck 2010](#)). Preterm birth is the single most important cause of infant mortality, and is associated with long-term serious disability in children, including cerebral palsy and sensory and cognitive impairments ([Elliott 2013](#); [Goldenberg 2008](#); [Pennell 2007](#)).

Even though the ability of obstetric care providers to identify women at risk of preterm birth has improved, the potential interventions for prevention of spontaneous preterm birth remain limited, and overall, the incidence of preterm deliveries has not decreased (Callaghan 2006). This is partly explained by the rise over the last decade in near-term births and those associated with medical complications, while early deliveries from spontaneous preterm labours have decreased (Ananth 2006; Goldenberg 2008). Recent evidence reports that about 30% to 50% of pregnant women with threatened preterm labour who had only bed rest developed recurrent preterm labour, and 30% of these women proceeded to deliver preterm (Chawanpaiboon 2009; Chawanpaiboon 2011; Varish 2005).

Many interventions have been introduced in an attempt to improve neonatal outcomes after preterm birth, including antepartum corticosteroid administration, exogenous surfactant therapy and new methods of mechanical ventilation. With the introduction of such interventions following very preterm birth or extremely preterm birth, neonates have more chances of survival, but they are at risk of neurological damage, and may face extended hospital stays (incurring high healthcare costs). Therefore, the prevention of preterm labour is very important to minimise or delay preterm birth. However, there is little definite evidence that interventions can prevent preterm labour or minimise preterm birth, and the goal is to identify preterm labour at the earliest possible time so that pregnancy prolongation can be obtained through acute and maintenance tocolysis. Pregnant women with threatened preterm labour at 34 weeks of gestation or less are usually treated with tocolytic therapy to inhibit uterine contractions. Tocolytics are used for at least 48 hours to allow corticosteroid administration to accelerate fetal lung maturity.

Therefore, in this review we were interested in assessing whether terbutaline pump maintenance therapy is effective in preventing preterm labour or minimising preterm birth, and in examining possible benefits or harms associated with this therapy.

Description of the intervention

Terbutaline is a beta-2 adrenergic receptor agonist, which has been used as a treatment for preterm labour. It is an off-label drug and is not approved by the Food and Drug Administration (FDA). It is a pregnancy category B medication prescribed to stop uterine contractions. In recent years, terbutaline has only rarely been used as an intravenous tocolytic to treat acute threatened preterm labour because of concerns about its safety (Elliott 2013). However, in some settings, subcutaneous terbutaline (0.25mg subcutaneous terbutaline) has been used as a single dose as a test for whether the woman will stop contractions (false labour); if true preterm labour (contractions less than five minutes with cervical dilatation) occurs, intravenous magnesium or atosiban, or oral nifedipine, or indomethacin (given orally, or as rectal suppositories) have been used as treatment (Valenzuela 2000). The aim of treatment is to

inhibit labour for at least 48 hours. This time can then be used to administer steroid injections to the mother, which help fetal lung maturity, or allow transfer to the appropriate level of care in an attempt to reduce complications of prematurity (Hofmeyr 2009). After successful tocolysis for threatened preterm labour, little evidence exists to show that oral terbutaline is effective for maintenance therapy (Goldenberg 2002), but subcutaneous terbutaline has been used as a maintenance tocolytic following initial treatment (Elliott 2013). A portable terbutaline pump, similar to an insulin pump, is used to infuse terbutaline subcutaneously. The initial minimum rate is started, increasing as needed to stop uterine contraction. When continuous terbutaline is administered via a programmable pump, with assessment of uterine contractions to individualise bolus therapy, significant pregnancy prolongation has been noted. However, both the basal infusion and bolus rates (four to six/24 hours - 0.25 mg) need to be determined in consultation with the pharmacist, taking account of weight, height, volume of distribution and renal clearance (Elliott 2013).

Terbutaline is easily absorbed subcutaneously and is not expensive. Pump therapy has the advantages over oral therapy because of lower total daily dose, fewer side effects and less tachycardia, faster onset of action and good tolerability (Elliott 2004; Perry 1995). Continuous subcutaneous terbutaline infusion has been associated with an extremely low incidence of serious adverse events (Elliott 2004; Perry 1995). On the other hand, high doses of terbutaline by the intravenous route have been associated with serious maternal side effects including pulmonary oedema, myocardial ischaemia, cardiac arrhythmias, hypotension and metabolic alterations, although women experiencing side effects may also had comorbid factors such as multi-fetal gestations, sepsis, pre-eclampsia, or cardiac arrhythmias (Iams 2009).

How the intervention might work

The rationale for maintenance therapy after threatened preterm labour for preventing preterm birth is based on a number of factors including (1) persistence of the underlying condition stimulating uterine contraction, as this may cause a recurrence; (2) an episode of recent uterine contraction may mean that the myometrium has a low threshold for recurrence; and (3) positive feedback from myometrial contractility can result in further contractions (Soloff 2000).

Therefore, maintenance tocolytic therapy with a terbutaline pump has been attempted to prolong pregnancy and decrease preterm birth. Home therapy is possible and stress from prolonged intravenous tocolysis decreased, although uterine contractions should continue to be assessed at home so that the bolus doses can be individualised and so that repeat episodes of preterm labour can be detected as early as possible (Elliott 2013).

Why it is important to do this review

Terbutaline has been used in clinical practice to inhibit uterine contractions, although in the United States, the FDA currently has not approved its use during pregnancy and there have been concerns about its use in pregnancy (FDA 2011). Previous evidence regarding the effectiveness of a terbutaline pump for maintenance therapy after successful tocolysis has been mixed and inconclusive (Hayes 2008). Two randomised controlled trials (Guinn 1998a; Wenstrom 1997a), involving 94 participants, of whom 39 used the terbutaline pump, did not show positive results. These trials were included in an earlier review (Nanda 2002). However, observational studies examining the use of subcutaneous terbutaline infusion have shown improvements in pregnancy prolongation, neonatal outcomes, and cost; Elliott 2013 summarised findings from 26 observational case control/cohort studies and 17 descriptive case series, involving over 24,000 women and reported positive findings relating to prolongation of pregnancy, gestational age at delivery, neonatal morbidity, and/or cost, which favoured women who had used terbutaline pump therapy. Perry 1995 and Elliott 2004 studied almost 18,000 women and found the incidence of adverse maternal effects to be similar in women whether or not they were exposed to subcutaneous terbutaline. This review replaces the earlier Cochrane review (Nanda 2002), which is no longer being updated by the team.

OBJECTIVES

To assess the effects of continuous low-dose subcutaneous terbutaline infusion maintenance therapy after threatened preterm labour for reducing adverse neonatal outcomes. Safety and adverse maternal and neonatal outcomes were also determined.

METHODS

Criteria for considering studies for this review

Types of studies

All published, unpublished and ongoing randomised controlled trials (including cluster-randomised trials) comparing outcomes between women given terbutaline pump maintenance therapy and controls given alternative therapy, placebo, or no therapy after successful arrest of threatened preterm labour. We did not include studies where allocation to groups was not truly random (e.g. allocation by day of the week).

We planned to include trials reported in abstracts if results were reported by randomisation group and provided sufficient infor-

mation was reported (or could be obtained from the authors) to allow us to assess risk of bias.

Types of participants

Pregnant women with intact membranes who had had at least one episode of threatened preterm labour that was halted by tocolytic therapy.

Types of interventions

Terbutaline pump maintenance therapy compared with alternative drug therapy, placebo, or no therapy.

Types of outcome measures

Primary outcomes

Reduction in serious neonatal morbidity and mortality.

Secondary outcomes

Neonatal

1. Preterm birth less than 37 completed weeks.
2. Very preterm birth (less than 34 completed weeks).
3. Extremely preterm birth (less than 28 completed weeks).
4. Gestational age at birth (not pre-specified).
5. Apgar score (not pre-specified).
6. Perinatal mortality.
7. Birthweight.
8. Respiratory distress syndrome.
9. Periventricular haemorrhage.
10. Need for mechanical ventilation.
11. Neurological sequelae (general intelligence, hearing, vision, cerebral palsy and disability).
12. Admission to neonatal intensive care unit at > 24 hours (not pre-specified timing).

Maternal

1. Cardiovascular complications (death, cardiac arrest, myocardial infarction, arrhythmia, hypotension).
2. Other serious complications (pulmonary oedema, hepatitis).
3. Side effects (chest pain, palpitations, shortness of breath, hyperglycaemia, hypokalaemia).
4. Maternal compliance with therapy (early discontinuation).
5. Maternal satisfaction of therapy.
6. Breastfeeding at hospital discharge.

Healthcare system

1. Rehospitalisation for threatened preterm labour.
2. Cost effectiveness of treatment.

Search methods for identification of studies

Electronic searches

We contacted the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register (31 January 2014).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
 2. weekly searches of MEDLINE;
 3. weekly searches of Embase;
 4. handsearches of 30 journals and the proceedings of major conferences;
 5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.
- Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).
- Trials identified through the search activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

Searching other resources

We reviewed citations of reference lists of included papers identified through the above search strategy and assessed their suitability for inclusion in the review.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors (Saifon Chawanpaiboon (SC) and Usanee Sangkomkamhang (US)) independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted another review author (Pisake Lumbiganon (PL)).

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors (SC and US) extracted the data using the agreed form. We resolved discrepancies through discussion with a third review author (Malinee Laopaiboon (ML)). We entered data into Review Manager software ([RevMan 2012](#)) and checked them for accuracy. When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Three review authors (SC, ML and PL) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We resolved any disagreement by discussion.

(1) Random sequence generation (checking for possible selection bias)

We have described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We have described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes; alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We have described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding would be unlikely to affect results. We

assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We have described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We have described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We have stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or supplied by the trial authors, we re-included missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We have described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- low risk of bias (where it was clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review were reported);
- high risk of bias (where not all the study's pre-specified outcomes were reported; one or more reported primary outcomes were not pre-specified; outcomes of interest were reported incompletely and so could not be used; study failed to

include results of a key outcome that would have been expected to have been reported);

- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We have described for each included study any important concerns we had about other possible sources of bias.

We assessed whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - see [Sensitivity analysis](#).

Measures of treatment effect

Dichotomous data

For dichotomous data, we have presented results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we used the mean difference as outcomes were measured in the same way between trials. We planned to use the standardised mean difference to combine trials that measured the same outcome, but used different methods.

Unit of analysis issues

We included only parallel individual randomised controlled trials in this review. The unit of analysis in all trials was women.

Cluster-randomised trials

We had planned to include cluster-randomised trials in the analyses along with individually-randomised trials if such trials were otherwise eligible. We did not identify any cluster-randomised trials. In updates of the review, if such trials are included we will adjust their sample sizes using the methods described in the *Cochrane Handbook* (Higgins 2011) using an estimate of the intracluster

correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform subgroup analysis to investigate the effects of the randomisation unit.

Cross-over trials

Cross-over trials are not a suitable design for this type of intervention and were therefore not eligible for inclusion.

Other unit of analysis issues

For trials with more than two arms (multi-arm trials), we planned to include data for all arms relevant to the scope of the review. Where appropriate, we would have combined arms (using methods described in the *Cochrane Handbook* (Higgins 2011)) to create a single pair-wise comparison. If it was not appropriate to combine arms, we would have presented results separately for each arm, sharing results for the control group between each to avoid double counting (for dichotomous outcomes we planned to divide the number of events and total sample by two, for continuous outcomes we would have assumed the same mean and standard deviation but halved the control sample size for each comparison). Wenstrom 1997b was the only included study with more than two arms.

We planned to include studies recruiting women with multiple pregnancies. We are aware that in multiple pregnancies outcomes for neonates are not independent; where sufficient information was available we planned therefore to adjust data for multiple pregnancies using the methods described in the *Cochrane Handbook* (Higgins 2011). In this version of the review included studies only recruited women with singleton pregnancies.

Dealing with missing data

For included studies, we noted levels of attrition and planned to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and all participants were analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention.

The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the τ^2 , I^2 and χ^2 statistics. We regarded heterogeneity as substantial if an I^2 was greater than 30% and either the τ^2 was greater than zero, or there was a low P value (less than 0.10) in the χ^2 test for heterogeneity. If we had identified substantial heterogeneity, we planned to explore it by pre-specified subgroup analysis (see *below*).

Assessment of reporting biases

In this version of the review very few data were pooled in meta-analyses. In future updates, in the unlikely event that there are 10 or more studies in a meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2012). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials examined the same intervention, and the trials' populations and methods were judged sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary, provided that an average treatment effect across trials was considered clinically meaningful.

Where we used random-effects analyses, the results have been presented as the average treatment effect with 95% confidence intervals, along with estimates of τ^2 and I^2 .

Subgroup analysis and investigation of heterogeneity

Had we identified substantial heterogeneity, we planned to investigate it using subgroup analyses. In this version of the review too few data were pooled in meta-analysis to allow meaningful subgroup analysis.

We planned to carry out the following subgroup analyses.

- Single versus multiple pregnancy

Any subgroup analysis in updates of the review will be restricted to the review's primary outcomes. We will assess subgroup differences by interaction tests available within RevMan (RevMan

[2012](#)). We will report the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

To test the robustness of results, we had planned to use sensitivity analyses to examine the effect of excluding studies at high risk of bias (such as from lack of allocation concealment) on the overall estimates of effect for primary outcomes. In view of the paucity of data in this version of the review we did not carry out these additional analyses.

R E S U L T S

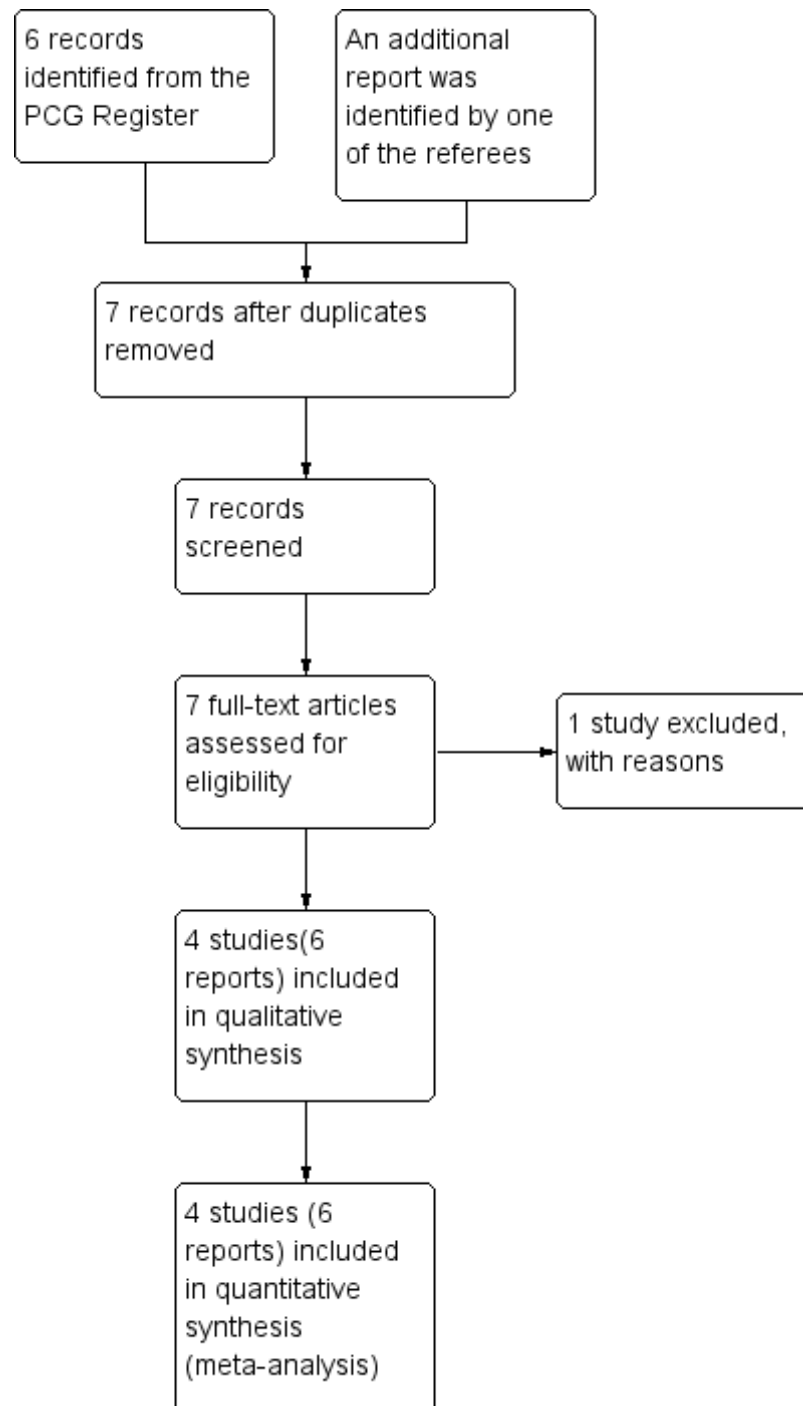
Description of studies

See [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

See: [Figure 1](#).

Figure 1.



The search of the Cochrane Pregnancy and Childbirth Group's Trials Register retrieved six reports corresponding to four studies (some studies resulted in more than one publication) and an additional report was identified by one of the referees.

Included studies

Four studies (Guinn 1998b; Lam 1988; Morales 1990; Wenstrom 1997b) involving 234 women were eligible for qualitative and quantitative synthesis (meta-analysis).

The published trial by Guinn 1998b and colleagues recruited 52 women with singleton gestations from 22 to less than 34 weeks of gestation with intact membranes who experienced suspected preterm labour that was arrested with intravenous magnesium sulfate therapy for at least 24 hours before study entry. The study was conducted in the USA. The authors calculated sample size a priori, and determined that a total sample size of 48 women in each group was needed to have 80% power to detect a clinically significant difference of a 14-day delay in the interval from treatment to birth between the two therapies. Guinn 1998b used a strict case definition of preterm labour. Women had to experience more than four uterine contractions per hour and at least one of the following: 80% or greater effacement, one centimetre or greater dilation, or documented cervical change. Terbutaline pump maintenance therapy was compared with saline placebo pump maintenance therapy. Both therapies used portable subcutaneous pumps (model 404-S; MiniMed Technologies, Sylmar, CA). Terbutaline therapy consisted of the continuous administration of 1 mg terbutaline/mL saline at the rate of 0.05 mL/hour with five daily bolus injections programmed at regular intervals. Women could also self-administer boluses of 0.25 mL twice daily for increased uterine activity. Saline placebo pump therapy was identical to terbutaline pump therapy except that saline replaced terbutaline. Women were followed up on a weekly basis during maintenance therapy, and nursing support was constantly available. In the event of recurrent preterm labour before 34 weeks of gestation, pump therapy was discontinued, and another course of intravenous magnesium therapy was given unless there was advanced cervical dilation or ruptured membranes. Pump maintenance therapy resumed if labour was arrested. Both pump therapies continued until either delivery or 36 weeks of gestation was reached.

The published trial by Lam 1988 randomised 68 women into one of two groups after women had completed their initial parenteral tocolysis. Thirty-five women (mean gestation 27.2 ± 3.4 weeks) received oral terbutaline 2.5 to 7.5 mg every two to four hours, and 33 women (mean gestation 28.2 ± 3.2 weeks) received terbutaline via a portable subcutaneous infusion pump starting at a basal rate of 0.03 to 0.05 mg/hour and intermittent boluses of 0.25 mg each. Using this regimen, the total daily terbutaline infusion was exceptionally low (< 3 mg/24 hours). An ambulatory tocodynamome-

ter recorded uterine activity data which was transmitted from the woman's home to the study centre daily. Oral and subcutaneous dosages were adjusted according to uterine activity. The primary outcome was birth at > 36 weeks' gestation. The ratio between the actual prolongation of pregnancy in weeks and the desired prolongation was expressed as the Pregnancy Prolongation Index (PPI). The two groups were compared according to the number of weeks gained in utero, the number of recurrent preterm labour episodes per woman, and the PPI.

The published trial by Morales 1990 recruited 72 women with less than 34 weeks' gestation following arrest of preterm labour. The study was conducted in the United States. The definition of preterm labour was progressive cervical change beyond one centimetre associated with regular uterine contractions. The two study groups were similar in terms of a variety of prematurity risk factors; urinary, cervical and intra-amniotic infections; gestational age on admission and cervical dilatation. Women were randomly assigned by sealed envelopes to either oral or pump therapy groups. Wenstrom 1997b and colleagues' published trial recruited 42 women with gestations from 20 to less than 35 weeks who had suspected preterm labour that was arrested with intravenous magnesium sulfate therapy for at least 48 hours before study entry. The authors did not describe sample size calculations. The study was conducted in the USA. Preterm labour was defined only as regular, persistent uterine contractions that produced observed cervical change. Three maintenance therapies were compared: terbutaline pump, saline placebo pump and oral terbutaline. Terbutaline pump and saline pump therapies used the same portable pump model as in the Guinn 1998b trial. The terbutaline pump group received 1 mg terbutaline/mL saline initially administered at rate of 0.05 mL/hour with 0.25 mL bolus injections every six hours. While the basal rate was kept constant, the bolus dose was adjusted to the women's unique contraction patterns. The saline placebo pump group received therapy identical to the terbutaline pump group except that saline replaced the terbutaline. The oral terbutaline group received 5 to 10 mg terbutaline orally every two to six hours, titrated to maintain maternal heart rate at 90 beats per minute or higher and to prevent uterine contractions from occurring at a rate of more than four per hour. If recurrent preterm labour occurred despite maximal therapy, the treatment arm assignment was determined and therapy was changed. Women receiving oral terbutaline or saline placebo therapy were switched to terbutaline pump, and women receiving terbutaline pump were switched to oral terbutaline. Women who had recurrent preterm labour that was not resolved after switching therapies were treated with intravenous tocolysis and aggressive management. Women were followed up on a weekly or biweekly basis according to the department's standard protocol for outpatient management of preterm labour. No gestational age was specified for

the discontinuation of therapy. The study authors attributed the low participation rate to women's concerns about the pump and its needle or the use of placebo. Physician reluctance to participate in the trial was not addressed. The treatment arm randomisation code was broken for women with recurrent preterm labour that could not be resolved with the assigned therapy. The assignment code was broken for nine of the 15 women in the terbutaline pump arm; one was switched to oral terbutaline, five received intravenous tocolytic therapy, and three delivered. The code was broken for eight of the 12 women in the saline placebo pump arm; three were switched to terbutaline pump, three received intravenous tocolytics, and two delivered. Two of the 15 women in the oral terbutaline

group received intravenous tocolytics. All cases were analysed on an intention-to-treat basis. The authors did not describe any cases of loss to follow-up.

Excluded studies

One study was excluded ([Morrison 1993](#)).

Risk of bias in included studies

Four studies ([Guinn 1998b](#); [Lam 1988](#); [Morales 1990](#); [Wenstrom 1997b](#)) were included; see [Figure 2](#) and [Figure 3](#) for summaries of the 'Risk of bias' assessments.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

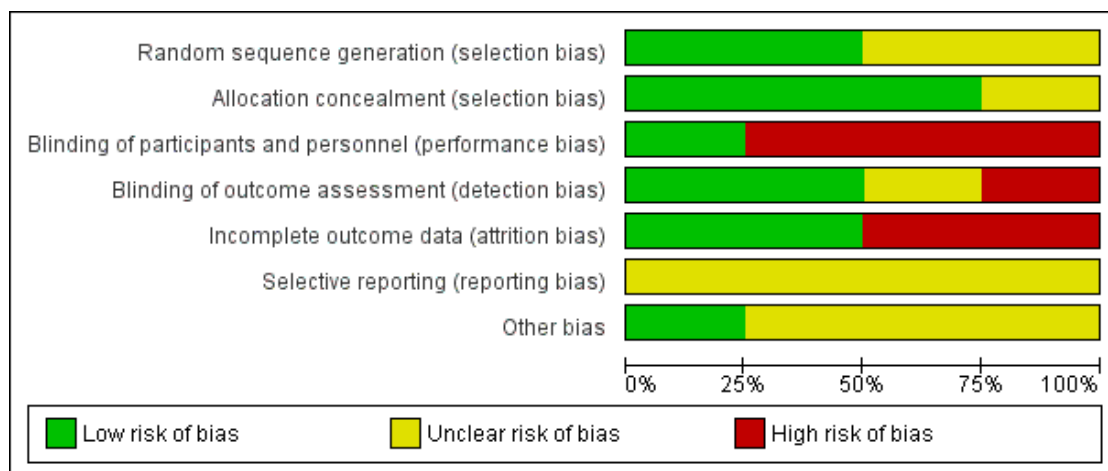


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Guinn 1998b	+	+	+	+	-	?	+
Lam 1988	?	?	-	-	+	?	?
Morales 1990	?	+	-	?	-	?	?
Wenstrom 1997b	+	+	-	+	+	?	?

Allocation

The [Guinn 1998b](#); [Morales 1990](#) and [Wenstrom 1997b](#) studies were assessed as at low risk of bias and [Lam 1988](#) was assessed as unclear.

Treatment allocation in the [Guinn 1998b](#) trial was based on computer-generated randomisation with stratification by cervical dilation (< 3 cm versus $\geq$ 3 cm) and previous indomethacin use.

No information was available in [Lam 1988](#).

In the [Morales 1990](#) trial, treatment allocation was randomly assigned by sealed envelopes to either oral or pump therapy groups. The pharmacist in the [Wenstrom 1997b](#) trial randomised women using a table of random numbers and prepared all solutions.

Blinding

[Guinn 1998b](#) was assessed as at low risk of bias and the [Lam 1988](#); [Morales 1990](#) and [Wenstrom 1997b](#) studies were assessed as high. In the [Guinn 1998b](#) trial, only the research pharmacist had knowledge of treatment assignment; the pharmacist prepared the pump solutions, which were clear, odourless, and indistinguishable. The interventions were not blinded to investigators and women in the [Lam 1988](#) trial.

Blinding was not mentioned in the [Morales 1990](#) study.

In the [Wenstrom 1997b](#) trial, the pump solutions were identical in appearance and only the pharmacist knew the pump assignments; however, the oral therapy was not blinded.

Incomplete outcome data

The [Lam 1988](#) and [Wenstrom 1997b](#) studies were assessed as at low risk of bias and the [Guinn 1998b](#) and [Morales 1990](#) studies were assessed as high risk of bias.

In the [Guinn 1998b](#) trial, there was a high dropout rate (38%) although an intention-to-treat analysis was carried out.

In the [Lam 1988](#) trial, all women appeared to be accounted for in the analyses.

About 15% (11 from 72 women) in the [Morales 1990](#) trial were lost to follow-up.

Over 90% of eligible women in the [Wenstrom 1997b](#) trial declined participation. There were no losses to follow-up.

Selective reporting

All studies ([Guinn 1998b](#); [Lam 1988](#); [Morales 1990](#) and [Wenstrom 1997b](#)) were assessed as at unclear risk of bias.

Assessing outcome reporting bias was difficult as we did not have access to study protocols. In two of the trials assessment was made from brief conference abstracts ([Lam 1988](#); [Morales 1990](#)).

Other potential sources of bias

The authors of the previous version of this review ([Nanda 2002](#)) wrote to the authors of two studies ([Guinn 1998b](#); [Wenstrom 1997b](#)) to request additional information on unreported outcomes. They also queried whether the numbers following the estimates in the tables, which were unlabeled, represented standard deviations. Since they did not receive a response from the authors, they assumed that the authors reported standard deviations.

In the [Wenstrom 1997b](#) trial several women crossed over into the other treatment arm (one woman from the terbutaline pump group to oral terbutaline group; and three from the saline pump group to the terbutaline pump).

Effects of interventions

Terbutaline pump versus saline placebo pump (two studies with 79 women)

Overall, there was insufficient evidence to determine whether or not terbutaline pump maintenance therapy was associated with a reduction in preterm birth or its complications compared with placebo. The small sample sizes of the two trials contributing data and the wide 95% confidence intervals for the outcomes reported meant that it was not possible to rule out either clinically important benefit or harm.

Primary outcome: Reduction in serious neonatal morbidity and mortality

No perinatal deaths were reported in either study included in this comparison ([Guinn 1998b](#); [Wenstrom 1997b](#)).

The [Guinn 1998b](#) study reported that no cases of intraventricular haemorrhage occurred. There was no clear evidence that respiratory distress syndrome (RDS) differed by treatment received ([Analysis 1.1](#)). Pooled data from the [Guinn 1998b](#) and [Wenstrom 1997b](#) trials showed a risk ratio (RR) of 0.82 (95% confidence interval (CI) 0.23 to 2.93, data for 79 infants) of RDS for terbutaline pump versus saline placebo pump.

Secondary outcomes

The [Guinn 1998b](#) trial found a RR of 1.17 (95% CI 0.79 to 1.73) of preterm birth ([Analysis 1.4](#)) and a RR of 0.97 (95% CI 0.51 to 1.84) of very preterm birth ([Analysis 1.3](#)) for terbutaline pump compared with saline placebo pump therapy. Preterm and very preterm birth were not reported in the other trial.

Both trials reported mean gestational age at birth; the difference between groups in gestational age at birth was small, although

the 95% CI was wide and did not exclude clinically important effects (mean difference (MD) -0.14 weeks, 95% CI -1.66 to 1.38) (Analysis 1.2).

There was insufficient evidence and inconclusive results for mean infant birthweight; the mean birthweight was not significantly different for terbutaline pump versus saline placebo pump groups when data from the Guinn 1998b and Wenstrom 1997b trials were combined but there was a wide 95% CI for this outcome (MD 107.72 g, 95% CI -216.65 to 432.09) (Analysis 1.5).

The Guinn 1998b study reported a RR of 0.94 (95% CI 0.51 to 1.73, 51 infants) for neonatal intensive care unit (NICU) stay greater than 24 hours (Analysis 1.6).

In the Wenstrom 1997b study, the authors reported no statistically significant differences in length of neonatal hospital stay between the terbutaline pump and saline placebo pump groups, and no differences between these groups for Apgar scores at one and five minutes (data not shown in data and analyses tables).

No data were available on need for mechanical ventilation or long-term neurological sequelae.

Neither of the trials reported serious complications of therapy. There was no clear evidence that terbutaline pump therapy resulted in a higher rate of therapy continuation (Analysis 1.7). For two trials, the RR of early discontinuation from assigned therapy was 1.15 (95% CI 0.68 to 1.95) for terbutaline pump compared with the saline placebo pump. The only cases of early discontinuation reported in the Wenstrom 1997b trial were those resulting from recurrent preterm labour that required the treatment assignment to be broken and therapy switched. Guinn 1998b described both discontinuations resulting from physician decisions (n = 9) as well as those resulting from women's choices (n = 11). No data were presented regarding costs.

Terbutaline pump versus oral terbutaline (three studies with 170 women)

The Lam 1988; Morales 1990 and Wenstrom 1997b trials included a comparison of terbutaline pump with oral terbutaline. For most outcomes there was insufficient evidence to draw conclusions about benefit or harm.

Primary outcome: Reduction in serious neonatal morbidity and mortality

No perinatal deaths were reported in any of the studies included in this comparison. We identified no clear difference in RDS (RR 1.00, 95% CI 0.16 to 6.20, one study, 30 infants) for the terbutaline pump compared with oral terbutaline (Analysis 2.1).

Secondary outcomes

The MD for gestational age at birth in one study was 1.40 weeks (95% CI -1.13 to 3.93) for terbutaline pump compared with oral

terbutaline therapy (Wenstrom 1997b) (Analysis 2.2). Mean infant birthweight was reported in one study and there was no evidence of a significant difference between groups: MD for birthweight was 484.00 g, 95% CI -25.00 to 993.00 for terbutaline pump versus oral terbutaline therapy (Analysis 2.3).

No statistically significant differences between the terbutaline pump and oral terbutaline pump arms in terms of Apgar scores at one and five minutes or length of neonatal hospital stay were identified in one study (non-prespecified outcomes, data not shown) (Wenstrom 1997b). No data were available on need for mechanical ventilation or long-term neurological sequelae. No difference was identified in early discontinuation with the terbutaline pump compared with oral terbutaline (RR 3.00, 95% CI 0.72 to 12.55) (Wenstrom 1997b) (Analysis 2.4).

The frequency of recurrent preterm labour was reported to be statistically significantly higher in the group of women receiving oral terbutaline therapy compared with the group receiving terbutaline infusion pump therapy ($P < 0.005$) (data not shown in the data and analysis) (Lam 1988).

In the study by Morales 1990, no statistically significant differences between therapy groups were reported in terms of number of re-admissions for intravenous tocolysis (mean 1.8 versus 1.2) (no standard deviations reported and data not shown in the data and analysis). There were no serious medical complications requiring discontinuation of either therapy in this study. Morales 1990 also reported that pump therapy resulted in significantly increased weekly costs/woman, mean \$580 versus \$12.50 ($P < 0.01$) (data not shown in data and analysis tables).

DISCUSSION

Summary of main results

There are insufficient data to be able to draw any firm conclusions about terbutaline pump maintenance therapy after threatened preterm labour for reducing adverse neonatal outcomes. The quality of the evidence is not high. The studies had small sample sizes and did not identify significant differences between groups receiving terbutaline pump maintenance therapy versus either placebo or oral therapy for any of our primary or secondary outcomes. Terbutaline pump maintenance therapy does not appear to offer any advantages over saline placebo pump, or oral terbutaline maintenance therapy in reducing adverse neonatal outcomes among women with arrested preterm labour. No trial found terbutaline pump therapy to be efficacious in reducing adverse neonatal outcomes, increasing gestational age at birth or in reducing preterm birth and its complications. Preliminary evidence indicated that pump therapy resulted in significantly increased weekly costs/woman.

Overall completeness and applicability of evidence

There are only four included studies which recruited 234 women; all four studies were conducted in United States. The available evidence was not sufficient to address all of the objectives of the review, and limits the external validity of results especially to low-resource settings.

All trials (Guinn 1998b; Lam 1988; Morales 1990; Wenstrom 1997b) had small sample sizes. The Guinn 1998b study only enrolled 52 women; however, the sample size was calculated to have sufficient power to detect a clinically significant difference (two weeks) between the two therapies in the interval from initiation of therapy to birth. The Wenstrom 1997b trial enrolled only 42 women despite a recruitment period of four years and four months. Over 90% of eligible women declined participation in the study. Although the authors state that no apparent differences existed between those who agreed to participate and those who declined, the possibility of differences cannot be eliminated. The Lam 1988 and Morales 1990 trials enrolled 68 and 72 women respectively, without explanation of the method of sample size calculation. All trials restricted enrolment to women with arrested preterm labour and, thus, at high risk for preterm birth. The ability to detect an association between terbutaline pump therapy and preterm birth, most likely, was strengthened by the exclusion of women with lower risk of preterm birth.

Elliott 2013 discussed the efficacy of continuous subcutaneous terbutaline infusion related to Wenstrom 1997b and Guinn 1998b and suggested that these studies had major flaws including low recruitment and small sample sizes. Elliott 2013 evinced that the bolus drug dosage administered in these two trials (Guinn 1998b; Wenstrom 1997b) was not altered based on end-organ response (uterine contraction) data, and this adjustment would be required if any benefit is to be achieved, but in these studies the research protocol did not include uterine contraction monitoring. Another problem in the design of these two studies is that the investigators did not use pharmacologic consultation regarding volume of distribution, body mass, renal clearance, and so forth to determine the appropriate basal dose of terbutaline for infusion, but rather all women (body mass index (BMI) 25 versus 45) received the same fixed dosage of the drug regardless BMI. Both trials were also underpowered (94 enrolled, 320 required by their power calculation) to show a difference from placebo.

Elliott 2013 also pointed out that the Guinn 1998b trial was also compromised by the high dropout rate: 41% in both arms of the study, (11 out of 24 women randomised to the terbutaline arm and nine of 28 women in the placebo arm. Wenstrom 1997b also concluded that a much larger study would be more likely to reveal some differences in outcome. In previous work, large observational studies, not randomised controlled trials, have suggested positive results of continuous subcutaneous terbutaline infusion therapy in pregnancy prolongation, neonatal outcome, and cost (Elliott 2004; Elliott 2013; Lam 1998; Perry 1995).

Considering the safety of terbutaline usage, the FDA changed the risk category of terbutaline from category B (no human or animal reproduction studies have demonstrated a fetal risk) to category C (animal reproduction studies have shown an adverse effect on the fetus). Elliott 2013 stated that the FDA used animal data from only one laboratory (Slotkin 2003) that was not replicated in other research studies to change the classification from B to C for terbutaline. More studies on the safety of terbutaline in humans are needed.

Quality of the evidence

All four included studies are under powered (Wenstrom 1997b) to show a difference between groups and there were high dropout rates of participants in Guinn 1998b. Two of the studies reported little information on study methods (Lam 1988; Morales 1990). Several women were crossed over into the other treatment arm in the Wenstrom 1997b trial.

The quality of the evidences is not strong enough to indicate whether or not terbutaline pump maintenance therapy after threatened preterm labour reduces adverse neonatal outcomes.

Potential biases in the review process

We strictly followed the review process recommended by the Cochrane Pregnancy and Childbirth Review Group to try to minimise bias in the review process. Two review authors independently assessed for inclusion all the potential studies we identified as a result of the search strategy. Two review authors independently extracted the data of the included studies using the agreed form. Three review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*.

Agreements and disagreements with other studies or reviews

We did not find any other trials (other than the four included studies) addressing this clinical problem. However, observational studies, not randomised controlled trials, suggest positive results for continuous subcutaneous terbutaline infusion therapy in pregnancy prolongation, neonatal outcome, and costs (Elliott 2004; Elliott 2013; Lam 1998; Perry 1995).

AUTHORS' CONCLUSIONS

Implications for practice

We identified no clear evidence that terbutaline pump maintenance therapy can decrease adverse neonatal outcomes by pro-

longing pregnancy. Taken together with the lack of evidence of benefit, its substantial expense and the lack of information on the safety of the therapy do not support its use in the management of arrested preterm labour. Terbutaline pump maintenance therapy should not be used outside well-designed randomised controlled trials.

Implications for research

Researchers who consider that the terbutaline pump might be an effective maintenance therapy should conduct adequately powered well-designed randomised controlled trials.

ACKNOWLEDGEMENTS

We would like to thank Kavita Nanda, Lynley A Cook, Maria F Gallo and David A Grimes for kindly preparing the previous version of this review (Nanda 2002).

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As part of the pre-publication editorial process, this review has been commented on by two peers (an editor and referee who is external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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Nanda K, Cook LA, Gallo MF, Grimes DA. Terbutaline pump maintenance therapy after threatened preterm labor for preventing preterm birth. *Cochrane Database of Systematic Reviews* 2002, Issue 4. [DOI: 10.1002/14651858.CD003933]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Guinn 1998b

Methods	RCT with 2 arms and individual randomisation.
Participants	52 women with singleton gestations and intact membranes from 22 to 33 6/7 weeks' gestation with preterm labour, defined as > 4 uterine contractions/hour and at least 1 of: ≥ 1 cm cervical dilation; ≥ 80% cervical effacement; documented cervical change. Only women who received magnesium sulfate therapy and had arrested labour (i.e. < 4 contractions/hour for ≥ 24 hours) were eligible. Exclusions included contraindications to tocolysis, persistent maternal tachycardia, history of cardiac arrhythmia, history of pulmonary oedema, uncontrolled diabetes, suspected chorioamnionitis
Interventions	1) Terbutaline pump group (n = 24) received 1 mg terbutaline/1 mL saline at 0.05 mL/hour with bolus injections 5 times daily. Participant could self-administer 0.25 mL twice daily for increased uterine activity. 2) Saline pump group (n = 28) received identical regimen to terbutaline pump group except terbutaline replaced with saline. Both groups received intensive education No electronic contraction monitoring or daily nursing contact. Advanced median cervical dilatation of 3 cm, effacement of 50% at start. Tocolytic therapy was not individualised for each woman
Outcomes	Primary outcome: mean interval time from initiation of maintenance therapy to birth. Secondary outcomes: episodes of recurrent preterm labour; birth < 37 weeks, birth < 34 weeks; GA at birth; mean birthweight; neonatal intensive care stay > 24 hours; respiratory distress syndrome; intraventricular haemorrhage; discontinuations from therapy
Notes	Sample size designed to have 80% power to detect a 2-week difference in time to birth

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation with stratification by cervical dilation (< 3 cm vs ≥ 3 cm) and previous indomethacin use
Allocation concealment (selection bias)	Low risk	Research pharmacist prepared identical pump solutions.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women and those providing care were described as masked and an intention-to-treat analysis was carried out although a number of women in both groups discontinued therapy

Guinn 1998b (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators were blinded in this double-blind placebo-controlled trial (it was not clear when the randomisation code was broken)
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall dropout rate was 38%. 13 women in the terbutaline group and 19 women in the placebo group completed this study. The study was under-powered in that it did not contain enough women to show a difference between groups. An intention-to-treat analysis was carried out for all women randomised as well as analysis for those women completing assigned therapy
Selective reporting (reporting bias)	Unclear risk	Our assessment was based on the published study report, we did not have access to the protocol
Other bias	Low risk	Other bias not apparent.

Lam 1988

Methods	RCT with 2 arms and individual randomisation.
Participants	68 women were randomised into one of two groups after completing their initial par- enteral tocolysis
Interventions	35 women received oral terbutaline (2.5 to 7.5 mg every 2-4 hours) and 33 women received a portable infusion pump which administered terbutaline subcutaneously at a basal rate of 0.03 to 0.05 mg/hour and intermittent boluses of 0.25 mg each. An ambulatory tocodynamometer recorded uterine activity data which was transmitted from the woman's home to the study centre daily. Oral and subcutaneous dosages were adjusted accordingly
Outcomes	The primary outcome was birth at > 36 weeks' gestation. The ratio between the actual prolongation of pregnancy in weeks and the desired prolongation was expressed as the Pregnancy Prolongation Index (PPI). The two groups were compared according to the number of weeks gained in utero, the number of recurrent preterm labour episodes per woman, and the PPI
Notes	Using this infusion pump regimen, authors reported that total daily terbutaline infusion was exceptionally low (< 3 mg/24 hours)

Risk of bias

Bias	Authors' judgement	Support for judgement

Lam 1988 (Continued)

Random sequence generation (selection bias)	Unclear risk	No information was available.
Allocation concealment (selection bias)	Unclear risk	No information was available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The interventions were not blinded to investigators and women
Blinding of outcome assessment (detection bias) All outcomes	High risk	It was stated that dosages of terbutaline were adjusted depending on uterine contraction
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women were accounted for in the analyses.
Selective reporting (reporting bias)	Unclear risk	Assessment based on brief conference abstract.
Other bias	Unclear risk	Little information on study methods.

Morales 1990

Methods	RCT with 2 arms and individual randomisation. There were randomly assigned by sealed envelopes to either oral or pump therapy groups	
Participants	72 women < 34 weeks' gestation following arrest of preterm labour defined as progressive cervical change beyond 1 cm associated with regular uterine contractions were eligible. However, data were available for only 61 women, 30 women with pump therapy and 31 women with oral therapy. The 2 study groups were equally divided and were similar in terms of a variety of prematurity risk factors; urine, cervical and intra-amniotic infections; GA on admission (29.4 vs 29.3 weeks), and cervical dilatation (2.0 vs 2.4 cm). 11 women were excluded post-randomisation without explanation	
Interventions	1) Subcutaneous terbutaline pump group (n = 30) vs 2) oral therapy group (n = 31) they received terbutaline with adjusted dosage to a maximum maternal pulse of 120 bpm No electronic contraction monitoring or daily nursing contact	
Outcomes	Time gained, proportion achieving term GA, number of re-admission for IV tocolysis, medical complication and cost	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Morales 1990 (Continued)

Random sequence generation (selection bias)	Unclear risk	No information was available.
Allocation concealment (selection bias)	Low risk	Randomisation by sealed envelopes to either oral or pump therapy groups
Blinding of participants and personnel (performance bias) All outcomes	High risk	The interventions were not blinded to investigators and women
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information was available.
Incomplete outcome data (attrition bias) All outcomes	High risk	72 women were randomised but results were reported for only 61
Selective reporting (reporting bias)	Unclear risk	Assessment based on published report we did not have access to the study protocol
Other bias	Unclear risk	Little information on study methods.

Wenstrom 1997b

Methods	RCT, 3 arms with individual randomisation.
Participants	42 women ≥ 20 to < 35 weeks' gestation with preterm labour, defined as with regular, persistent uterine contractions with cervical change. Only women who received IV magnesium sulfate therapy and, if needed, oral indomethacin and had arrested labour were eligible. Exclusions included contraindications to betamimetics, contraindications to tocolysis; cervical dilation > 4 cm
Interventions	(1) Terbutaline pump group (n = 15) received 1 mg terbutaline/1 mL saline at 0.05 mL/hour with 0.25 bolus injections every 6 hours. Bolus dose adjusted to women's contraction pattern. (2) Saline pump group (n = 12) received identical regimen to terbutaline pump group except terbutaline replaced with saline. (3) Oral terbutaline group (n = 15) received 5 to 10 mg terbutaline orally every 2-6 hours titrated to keep maternal heart rate ≥ 90 bpm and to keep uterine contractions to ≤ 4 /hour. All groups placed on bedrest
Outcomes	Mean GA at birth; mean birthweight; drug boluses required; net gain in weeks; median Apgar scores; length of infant hospital stay; antenatal complications; neonatal complications
Notes	Over 90% of eligible women declined participation. If recurrent preterm labour occurred despite maximisation of therapy, code was broken and therapy was changed (9 women in terbutaline group; 8 women in saline group). Study Table 1 reports 8 mothers with twins,

	but neonatal complications reported using denominator of number of participants per group	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by random-number table.
Allocation concealment (selection bias)	Low risk	Randomisation by pharmacist. Pharmacist prepared identical solutions and oral therapy
Blinding of participants and personnel (performance bias) All outcomes	High risk	Women, investigators, and outcome assessors masked to the 2 pump therapies but not oral therapy. It was stated that it was necessary to “unblind” the group assignments for 9/15 of women in the terbutaline pump woman and 8/12 of those in the saline pump group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	It was stated that group assignments were not available to investigators until after birth
Incomplete outcome data (attrition bias) All outcomes	Low risk	Although several women did not receive treatment according to protocol there appeared to be an intention-to-treat analysis with outcomes reported according to randomisation group
Selective reporting (reporting bias)	Unclear risk	Assessment based on published report. We did not have access to the study protocol
Other bias	Unclear risk	Several women crossed over into the other treatment arm.

bpm: beats per minute

GA: gestational age

IV: intravenous

RCT: randomised controlled trials

vs: versus

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Morrison 1993	We did not have sufficient information on this study to assess eligibility for inclusion

DATA AND ANALYSES

Comparison 1. Terbutaline pump versus saline pump

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Respiratory distress syndrome	2	79	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.23, 2.93]
2 Gestational age at birth (in weeks)	2	79	Mean Difference (IV, Random, 95% CI)	-0.14 [-1.66, 1.38]
3 Very preterm birth (< 34 weeks)	1	52	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.51, 1.84]
4 Preterm birth (< 37 weeks)	1	52	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.79, 1.73]
5 Birthweight	2	79	Mean Difference (IV, Fixed, 95% CI)	107.72 [-216.65, 432.09]
6 Neonatal intensive care unit admissions at > 24 hours	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.51, 1.73]
7 Early discontinuation	2	79	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.68, 1.95]

Comparison 2. Terbutaline pump versus oral terbutaline

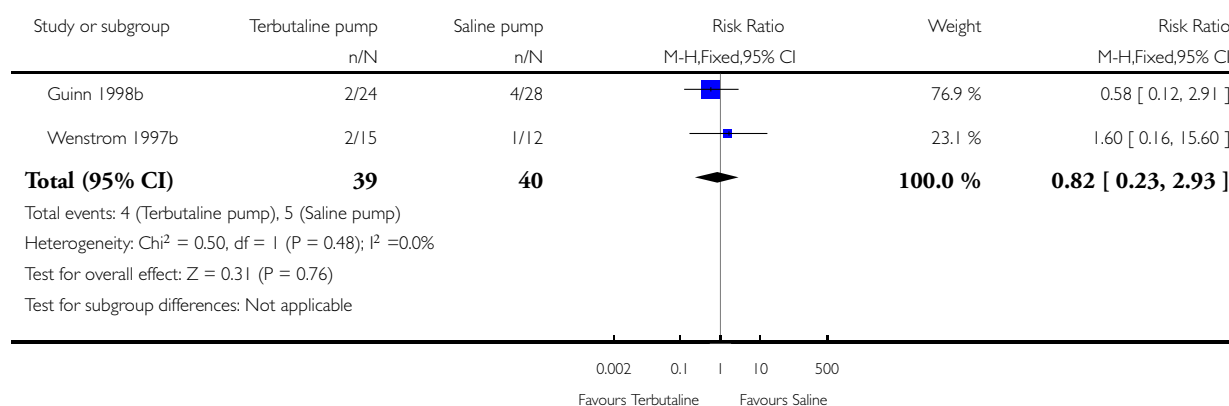
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Respiratory distress syndrome	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.16, 6.20]
2 Gestational age at birth (in weeks)	1	30	Mean Difference (IV, Fixed, 95% CI)	1.40 [-1.13, 3.93]
3 Birthweight	1	30	Mean Difference (IV, Fixed, 95% CI)	484.0 [-25.00, 993.00]
4 Early discontinuation	1	30	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.72, 12.55]

Analysis 1.1. Comparison 1 Terbutaline pump versus saline pump, Outcome 1 Respiratory distress syndrome.

Review: Terbutaline pump maintenance therapy after threatened preterm labour for reducing adverse neonatal outcomes

Comparison: 1 Terbutaline pump versus saline pump

Outcome: 1 Respiratory distress syndrome

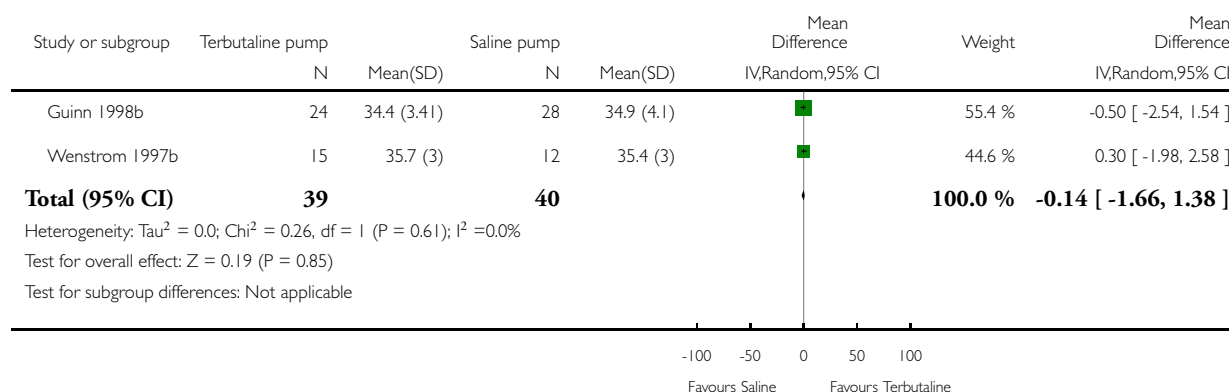


Analysis 1.2. Comparison 1 Terbutaline pump versus saline pump, Outcome 2 Gestational age at birth (in weeks).

Review: Terbutaline pump maintenance therapy after threatened preterm labour for reducing adverse neonatal outcomes

Comparison: 1 Terbutaline pump versus saline pump

Outcome: 2 Gestational age at birth (in weeks)

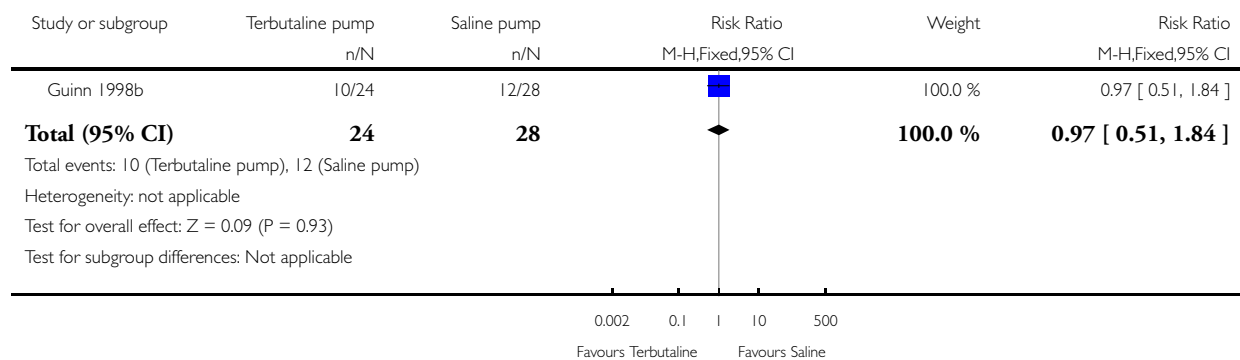


Analysis 1.3. Comparison 1 Terbutaline pump versus saline pump, Outcome 3 Very preterm birth (< 34 weeks).

Review: Terbutaline pump maintenance therapy after threatened preterm labour for reducing adverse neonatal outcomes

Comparison: 1 Terbutaline pump versus saline pump

Outcome: 3 Very preterm birth (< 34 weeks)

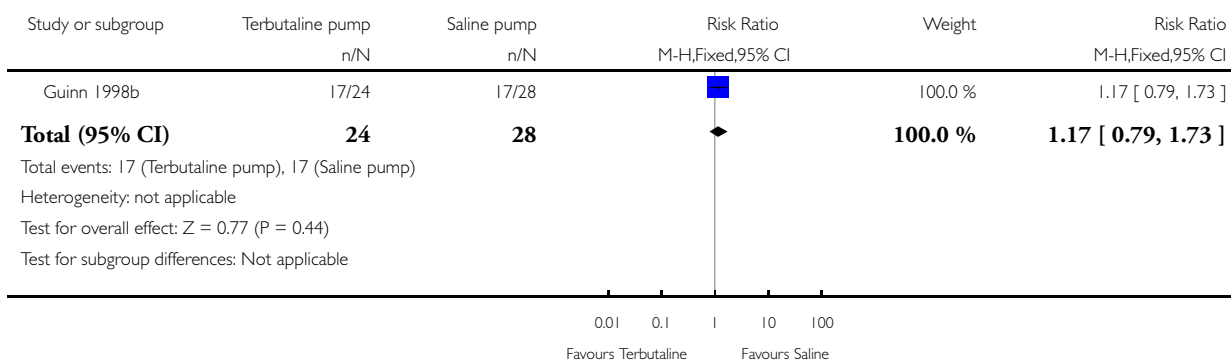


Analysis 1.4. Comparison 1 Terbutaline pump versus saline pump, Outcome 4 Preterm birth (< 37 weeks).

Review: Terbutaline pump maintenance therapy after threatened preterm labour for reducing adverse neonatal outcomes

Comparison: 1 Terbutaline pump versus saline pump

Outcome: 4 Preterm birth (< 37 weeks)

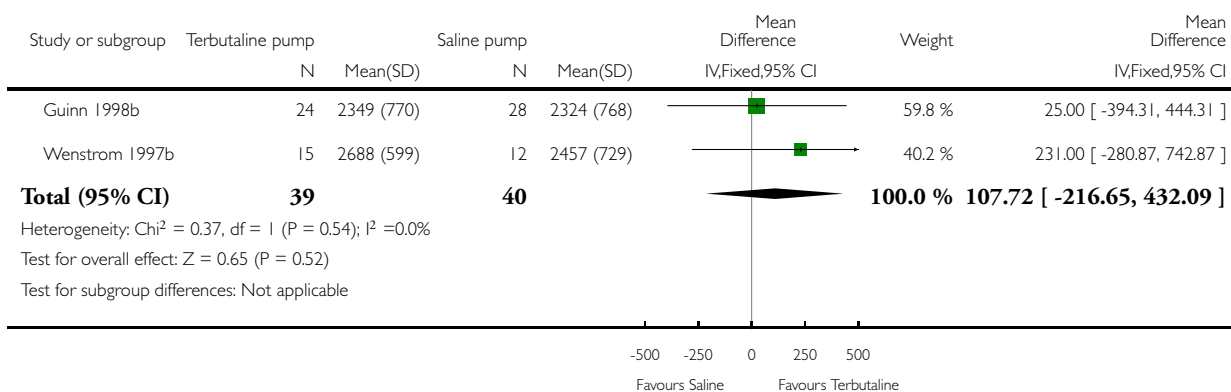


Analysis 1.5. Comparison 1 Terbutaline pump versus saline pump, Outcome 5 Birthweight.

Review: Terbutaline pump maintenance therapy after threatened preterm labour for reducing adverse neonatal outcomes

Comparison: 1 Terbutaline pump versus saline pump

Outcome: 5 Birthweight

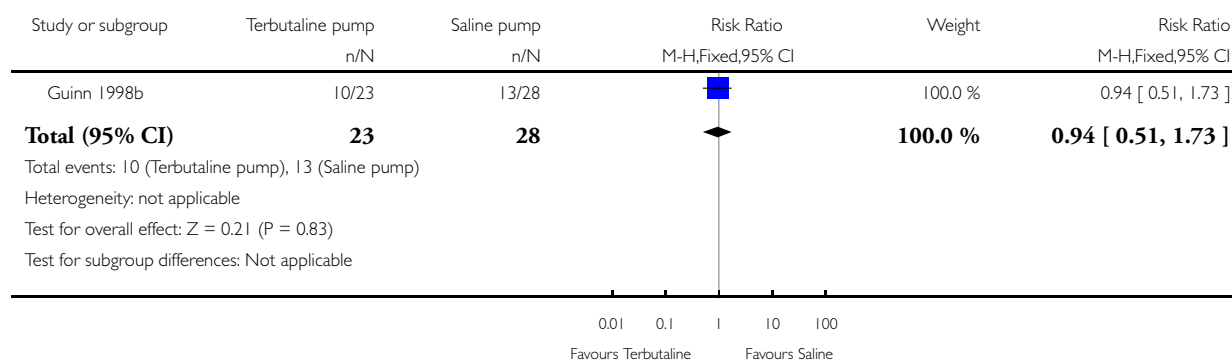


Analysis 1.6. Comparison 1 Terbutaline pump versus saline pump, Outcome 6 Neonatal intensive care unit admissions at > 24 hours.

Review: Terbutaline pump maintenance therapy after threatened preterm labour for reducing adverse neonatal outcomes

Comparison: 1 Terbutaline pump versus saline pump

Outcome: 6 Neonatal intensive care unit admissions at > 24 hours

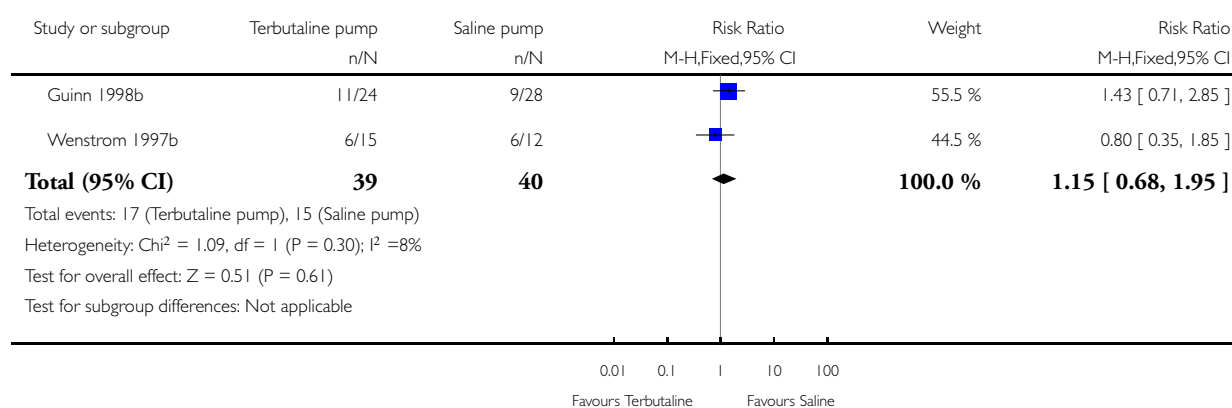


Analysis 1.7. Comparison 1 Terbutaline pump versus saline pump, Outcome 7 Early discontinuation.

Review: Terbutaline pump maintenance therapy after threatened preterm labour for reducing adverse neonatal outcomes

Comparison: 1 Terbutaline pump versus saline pump

Outcome: 7 Early discontinuation

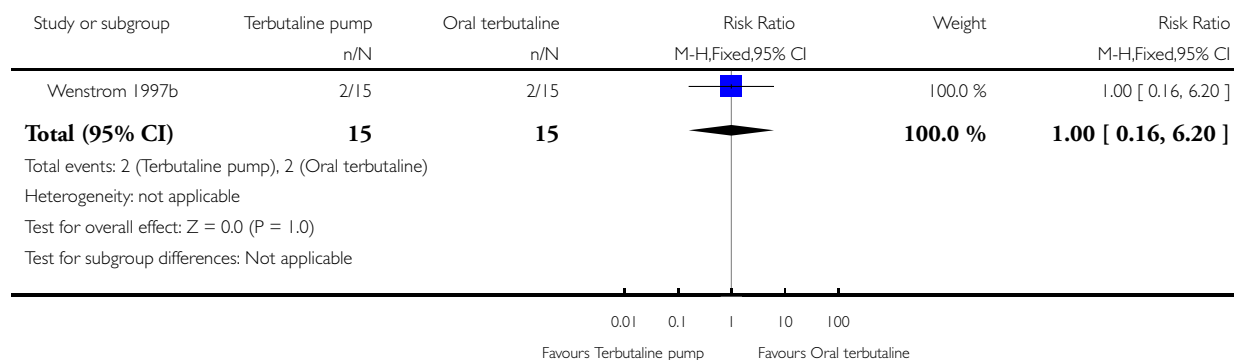


Analysis 2.1. Comparison 2 Terbutaline pump versus oral terbutaline, Outcome 1 Respiratory distress syndrome.

Review: Terbutaline pump maintenance therapy after threatened preterm labour for reducing adverse neonatal outcomes

Comparison: 2 Terbutaline pump versus oral terbutaline

Outcome: 1 Respiratory distress syndrome

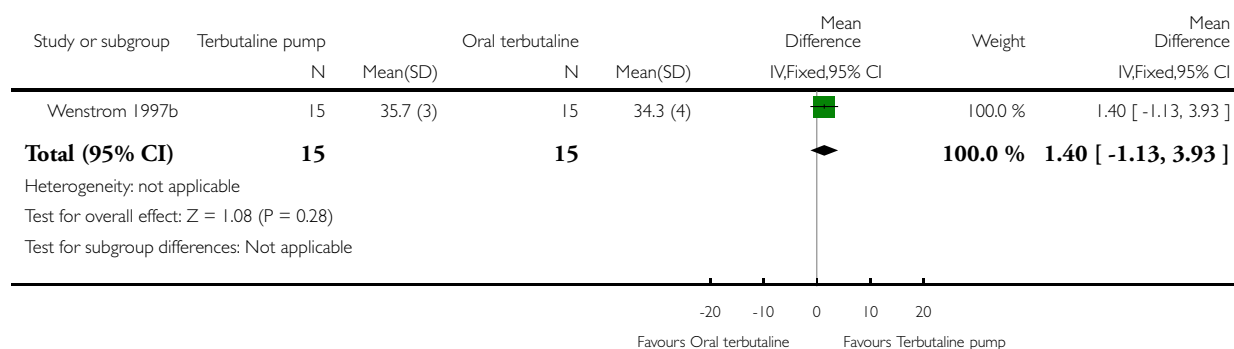


Analysis 2.2. Comparison 2 Terbutaline pump versus oral terbutaline, Outcome 2 Gestational age at birth (in weeks).

Review: Terbutaline pump maintenance therapy after threatened preterm labour for reducing adverse neonatal outcomes

Comparison: 2 Terbutaline pump versus oral terbutaline

Outcome: 2 Gestational age at birth (in weeks)

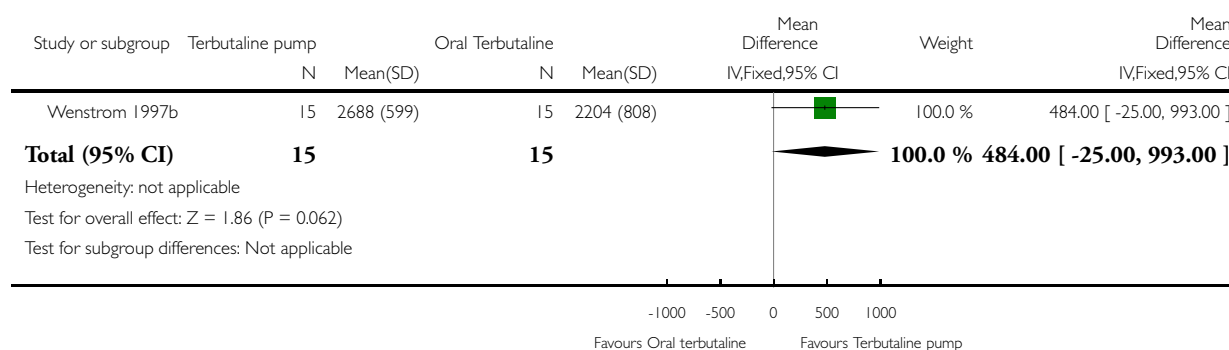


Analysis 2.3. Comparison 2 Terbutaline pump versus oral terbutaline, Outcome 3 Birthweight.

Review: Terbutaline pump maintenance therapy after threatened preterm labour for reducing adverse neonatal outcomes

Comparison: 2 Terbutaline pump versus oral terbutaline

Outcome: 3 Birthweight

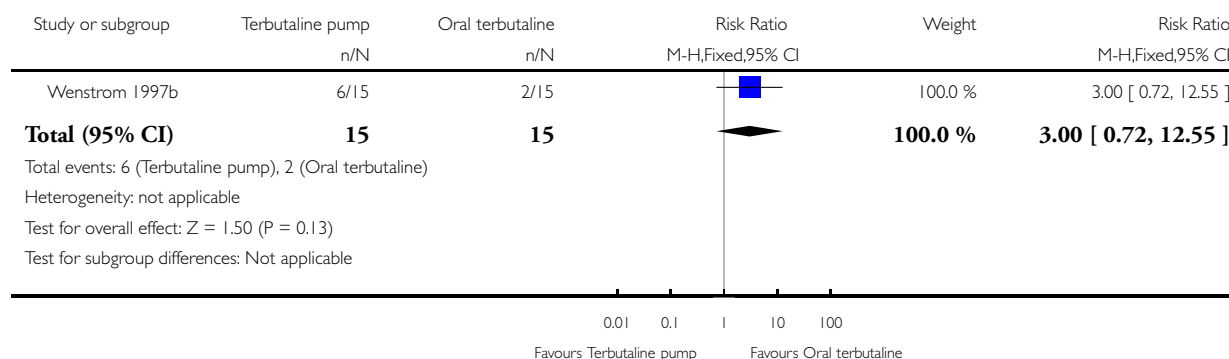


Analysis 2.4. Comparison 2 Terbutaline pump versus oral terbutaline, Outcome 4 Early discontinuation.

Review: Terbutaline pump maintenance therapy after threatened preterm labour for reducing adverse neonatal outcomes

Comparison: 2 Terbutaline pump versus oral terbutaline

Outcome: 4 Early discontinuation



CONTRIBUTIONS OF AUTHORS

Saifon Chawanpaiboon, Malinee Laopaiboon, Pisake Lumbiganon and Ussanee Sangkomkarnhang drafted the protocol and the review. All review authors revised and approved the final version of the protocol and review. Therese Dowswell finalised the drafts for editorial approval.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Faculty of Medicine, Siriraj Hospital, Mahidol University, Thailand.
- Faculty of Medicine, Khon Kaen University, Thailand.
- Faculty of Public Health, Khon Kaen University, Thailand.
- Khon Kaen Hospital, Ministry of Public Health, Thailand.
- University of Liverpool, UK.

External sources

- Thai Cochrane Network, Australasian Cochrane Centre, Thailand.
- UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research (RHR), World Health Organization, Switzerland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added two outcomes not prespecified in the protocol (Apgar score less than seven at five minutes, and mean gestational age at birth).

NOTES

This review replaces the earlier review ([Nanda 2002](#)), which is no longer being updated by the team.

INDEX TERMS

Medical Subject Headings (MeSH)

Gestational Age; Maintenance Chemotherapy [*methods]; Obstetric Labor, Premature [drug therapy; *prevention & control]; Premature Birth [prevention & control]; Randomized Controlled Trials as Topic; Secondary Prevention; Terbutaline [*administration & dosage]; Tocolytic Agents [*administration & dosage]

MeSH check words

Female; Humans; Pregnancy



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Vaginal chlorhexidine during labour for preventing maternal and neonatal infections (excluding Group B Streptococcal and HIV) (Review)

Lumbiganon P, Thinkhamrop J, Thinkhamrop B, Tolosa JE

Lumbiganon P, Thinkhamrop J, Thinkhamrop B, Tolosa JE.

Vaginal chlorhexidine during labour for preventing maternal and neonatal infections (excluding Group B Streptococcal and HIV).

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	3
BACKGROUND	5
OBJECTIVES	5
METHODS	6
RESULTS	8
Figure 1.	9
Figure 2.	10
DISCUSSION	12
AUTHORS' CONCLUSIONS	12
ACKNOWLEDGEMENTS	12
REFERENCES	13
CHARACTERISTICS OF STUDIES	15
DATA AND ANALYSES	21
Analysis 1.1. Comparison 1 Chlorhexidine vaginal wash versus placebo, Outcome 1 Chorioamnionitis.	21
Analysis 1.2. Comparison 1 Chlorhexidine vaginal wash versus placebo, Outcome 2 Postpartum endometritis.	22
Analysis 1.3. Comparison 1 Chlorhexidine vaginal wash versus placebo, Outcome 3 Side effects.	22
Analysis 1.4. Comparison 1 Chlorhexidine vaginal wash versus placebo, Outcome 4 Neonatal pneumonia.	23
Analysis 1.5. Comparison 1 Chlorhexidine vaginal wash versus placebo, Outcome 5 Neonatal meningitis.	24
Analysis 1.6. Comparison 1 Chlorhexidine vaginal wash versus placebo, Outcome 6 Blood culture confirming neonatal sepsis.	24
Analysis 1.7. Comparison 1 Chlorhexidine vaginal wash versus placebo, Outcome 7 Neonatal sepsis.	25
Analysis 1.8. Comparison 1 Chlorhexidine vaginal wash versus placebo, Outcome 8 Perinatal mortality.	25
Analysis 1.9. Comparison 1 Chlorhexidine vaginal wash versus placebo, Outcome 9 Newborn received antibiotics.	26
APPENDICES	26
WHAT'S NEW	30
HISTORY	30
CONTRIBUTIONS OF AUTHORS	31
DECLARATIONS OF INTEREST	31
SOURCES OF SUPPORT	31
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	32
NOTES	32
INDEX TERMS	32

[Intervention Review]

Vaginal chlorhexidine during labour for preventing maternal and neonatal infections (excluding Group B Streptococcal and HIV)

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ABSTRACT

Background

The incidence of chorioamnionitis occurs in between eight and 12 women for every 1000 live births and 96% of cases of chorioamnionitis are due to ascending infection. Following spontaneous vaginal delivery, 1% to 4% of women develop postpartum endometritis. The incidence of neonatal sepsis is 0.5% to 1% of all infants born. Maternal vaginal bacteria are the main agents for these infections. It is reasonable to speculate that prevention of maternal and neonatal infections might be possible by washing the vagina and cervix with an antibacterial agent for all women during labour. Chlorhexidine belongs to the class of compounds known as the bis-biguanides. Chlorhexidine has antibacterial action against a wide range of aerobic and anaerobic bacteria, including those implicated in periparturient infections.

Objectives

To evaluate the effectiveness and side effects of chlorhexidine vaginal douching during labour in reducing maternal and neonatal infections (excluding group B streptococcal and HIV).

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 June 2014), reference lists of retrieved reports and journal letters and editorials.

Selection criteria

Randomized or quasi-randomized trials comparing chlorhexidine vaginal douching during labour with placebo or other vaginal disinfectant to prevent (reduce) maternal and neonatal infections (excluding group B streptococcal and HIV).

Data collection and analysis

Two review authors independently assessed trial eligibility and quality, extracted and interpreted the data. A third review author analyzed and interpreted the data. The fourth author also interpreted the data.

Vaginal chlorhexidine during labour for preventing maternal and neonatal infections (excluding Group B Streptococcal and HIV)
(Review)

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Main results

We included three studies (3012 participants). There was no evidence of an effect of vaginal chlorhexidine during labour in preventing maternal and neonatal infections. Although the data suggest a trend in reducing postpartum endometritis, the difference was not statistically significant (three trials, 3012 women, risk ratio 0.83; 95% confidence interval 0.61 to 1.13).

Assessment of the quality of the evidence using GRADE indicated that the levels of evidence for all primary outcomes and one important secondary outcome were low to moderate.

Authors' conclusions

There is no evidence to support the use of vaginal chlorhexidine during labour in preventing maternal and neonatal infections. There is a need for a well-designed randomized controlled trial using appropriate concentration and volume of vaginal chlorhexidine irrigation solution and with adequate sample size.

PLAIN LANGUAGE SUMMARY

Vaginal chlorhexidine during labour for preventing maternal and neonatal infections (excluding group B streptococcal and HIV)

Bacteria live in women's vaginas and generally cause no problems. Very occasionally they infect the placenta during labour and can pass to the baby, causing an infection. These infections can occasionally make the baby very ill and very occasionally the baby might die.

The review of three trials (3012 participants) found there was not enough information to say whether the use of chlorhexidine washing of the vagina during labour led to fewer infections for mothers and babies. More research is needed.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Chlorhexidine vaginal wash versus placebo for preventing maternal and neonatal infections (excluding Group B Streptococcal and HIV)						
Population: Pregnant women with a gestational age greater than 28 weeks, considered to be in labour receiving chlorhexidine vaginal douching during labour versus placebo to prevent maternal and neonatal infections (excluding Group B Streptococcal and HIV).						
Settings: Hospitals in the United States.						
Intervention: Chlorhexidine vaginal douching during labour versus placebo or other vaginal disinfectant						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Chlorhexidine vaginal wash versus placebo				
Chorioamnionitis Clinical findings	Study population		RR 1.1 (0.86 to 1.42)	3012 (3 studies)	⊕⊕⊕○ moderate ¹	
	69 per 1000	76 per 1000 (59 to 98)				
	Moderate					
	62 per 1000	68 per 1000 (53 to 88)				
Postpartum endometritis Clinical findings	Study population		RR 0.83 (0.61 to 1.13)	3012 (3 studies)	⊕⊕⊕○ moderate ¹	
	57 per 1000	47 per 1000 (35 to 64)				
	Moderate					
	72 per 1000	60 per 1000 (44 to 81)				

Neonatal sepsis Clinical findings	Study population		RR 0.75 (0.17 to 3.35)	2987 (3 studies)	⊕⊕○○ low ²
	3 per 1000	2 per 1000 (0 to 9)			
	Moderate				
	4 per 1000	3 per 1000 (1 to 13)			
Blood culture confirm- ing neonatal sepsis Clinical findings and confirmation by labora- tory	Study population		RR 0.75 (0.17 to 3.35)	2077 (2 studies)	⊕⊕○○ low ²
	4 per 1000	3 per 1000 (1 to 13)			
	Moderate				
	4 per 1000	3 per 1000 (1 to 13)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Confidence interval crossing the line of no effect.

² Wide confidence interval crossing the line of no effect & few events.

BACKGROUND

Description of the condition

Chorioamnionitis is an inflammatory reaction of the placental tissues in response to organism invasion. The incidence of chorioamnionitis occurs in eight to 12 women for every 1000 live births and 96% of the cases of chorioamnionitis are due to an ascending infection (Monif 1993). Following spontaneous vaginal delivery, 1% to 4% of women develop postpartum endometritis (Monif 1993). Although uterine infections are relatively uncommon following uncomplicated vaginal delivery, they continue to be a major problem in women delivered by caesarean section. Vaginal examinations increase the risk of inoculation and colonization of lower uterine incisions and laceration and therefore increase the risk of postpartum endometritis in women delivered by caesarean section (Cunningham 2001).

Bacterial infection is an important cause of neonatal morbidity and mortality. A prospective study from Pakistan reported a prevalence of blood culture proven bacterial sepsis to be 5.6 per 1000 live births (Bhutla 1997). Septicemia accounted for 11% to 30.4% of all neonatal deaths (Boo 1994). Other forms of infection include ophthalmia neonatorum; neonatal pneumonia and neonatal meningitis. Maternal vaginal bacteria are the main agents for these infections.

Description of the intervention

It is reasonable to speculate that prevention of maternal and neonatal infections might be possible by washing the vagina and cervix with an antibacterial agent in women during labour. Vaginal and cervical washing is usually performed by gently introducing a catheter attached to a 50 to 60 mL syringe up to the cervix. The cervical area is flushed with 50 to 60 mL of the solution. The syringe is then refilled without removing the catheter, and a second flushing with the same amount of the solution is performed while slowly withdrawing the catheter (Gaillard 2001). This procedure can be performed within a few minutes and would not interfere with women's labour when they wish to move and adopt a position which they feel is right for them. To be clinically useful, such an agent would need to possess antimicrobial activity against a broad range of bacteria that have been implicated in periparturient infection, be non-toxic and non-irritating for mother and fetus/neonate. Ideally, the agent would be inexpensive and commercially available. Chlorhexidine, a widely used medical disinfectant, satisfies these requirements.

How the intervention might work

Chlorhexidine belongs to the class of compounds known as the bis-biguanides. Because of its high cationic nature, it has a strong

affinity for the cell wall of micro-organisms, to which it binds, disrupting osmotic equilibrium. The disrupted cytoplasmic membrane precipitates intracellularly, preventing repair of the cell wall and eventually resulting in cell death (Davies 1973). These actions endow chlorhexidine with antibacterial action against a wide range of aerobic and anaerobic bacteria, including those implicated in periparturient infections (Emilson 1977; Hennessey 1973). This antibacterial action is achieved at a very low concentration: typical minimum inhibitory concentrations are in microgram (mcg) per millilitre (mL), whereas clinically used concentrations are in milligram (mg) per mL. A randomized controlled trial demonstrated that vaginal douching with chlorhexidine during labour can significantly reduce maternal and early neonatal (including group B streptococcal) infection (Stray-Pedersen 1999). Finally, complete resistance to chlorhexidine rarely emerges even after long-term use (Ferretti 1990).

The allergic and toxic potential of chlorhexidine is very low. For many decades, chlorhexidine has been the major medical skin and the mucous membrane disinfectant in use. Despite its widespread use, only individual cases of anaphylactic or even mild allergic reactions in exposed medical personnel have been reported (Bergqvist-Karlsson 1988). Chlorhexidine tends not to be absorbed by human skin and mucous membrane barrier (Johnsson 1987; Nilsson 1989). A long-term human oral safety trial did not show any systemic or serious local side effects after two years of continuous use (Johnsson 1987). In contrast to povidone-iodine, vaginally applied chlorhexidine was not absorbed in measurable amounts into the blood stream (Vorherr 1984).

Why it is important to do this review

Maternal and neonatal infections occur commonly and have serious ramifications for both mothers and newborns. Vaginal chlorhexidine douching may offer a safe, inexpensive, and theoretically sound approach to prevent maternal and neonatal infections. Vaginal disinfection during labour for reducing the risk of mother-to-child transmission (MTCT) of HIV infection is addressed in one Cochrane review which indicated that there was no evidence of an effect of vaginal disinfection on MTCT of HIV (Waysong 2005). Another Cochrane review also does not support the use of vaginal chlorhexidine during labour to prevent early-onset neonatal group B streptococcal infection (Stade 2008).

OBJECTIVES

To evaluate the effectiveness and side effects of chlorhexidine vaginal douching during labour in reducing maternal and neonatal infections (excluding group B streptococcal and HIV).

METHODS

Criteria for considering studies for this review

Types of studies

Randomized, quasi-randomized or cluster-randomized trials comparing chlorhexidine vaginal douching during labour with placebo or other vaginal disinfectant to prevent (reduce) maternal and neonatal infections (excluding group B streptococcal and HIV).

Types of participants

All pregnant women with a gestational age greater than 28 weeks, considered to be in labour.

Types of interventions

Chlorhexidine vaginal douching during labour versus placebo or other vaginal disinfectant.

Types of outcome measures

Primary outcomes

1. Maternal outcomes

- (a) Chorioamnionitis (variously defined by the authors);
- (b) postpartum endometritis (variously defined by the authors).

2. Neonatal outcomes

- (a) Neonatal sepsis (variously defined by the authors).

Secondary outcomes

1. Maternal outcomes

- (a) Intrapartum fever;
- (b) intrapartum treatment with antibiotics;
- (c) maternal side effects (vaginal irritation, thrush, antimicrobial resistance);
- (d) serious maternal complication of treatment (e.g. anaphylaxis);
- (e) laparotomy for infection;
- (f) hysterectomy;
- (g) maternal death;
- (h) satisfaction with care;
- (i) length of hospital stay;
- (j) postnatal depression;
- (k) successful breastfeeding (variously defined by the authors);
- (l) costs of care;
- (m) antimicrobial resistance.

2. Neonatal outcomes

- (a) Ophthalmia neonatorum;
- (b) neonatal pneumonia by clinical assessment and/or chest X-ray;
- (c) neonatal meningitis by clinical assessment and/or culture;
- (d) blood culture confirming sepsis;
- (e) admission to neonatal intensive care unit;
- (f) length of hospital stay;
- (g) perinatal mortality;
- (h) abnormal neurodevelopmental assessment at follow-up.

Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (30 June 2014).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of Embase;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

[For details of additional author searching carried out the previous version of the review ([Lumbiganon 2004](#)), please see [Appendix 1](#).]

Searching other resources

We searched cited references from retrieved articles for additional studies. We reviewed abstracts and letters to the editor to identify randomized controlled trials that had not been published and reviewed editorials, indicating expert opinion, to identify and ensure that no key studies were missed for consideration for inclusion in this review.

We did not apply any language restrictions.

Data collection and analysis

For the methods used when assessing the trials identified in the previous version of this review, see [Lumbiganon 2004](#).

For this update, two new studies were identified and excluded ([Pereira 2011](#); [Saleem 2006](#)). We will use the methods outlined in [Appendix 2](#) for new trials identified at the next update.

We used the following updated methods to assess the risk of bias and assess the quality of already included studies using the GRADE approach. The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Two review authors (PL and JT) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We resolved any disagreement by discussion or by involving the third review author (JET).

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal the allocation sequence and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies

were at low risk of bias if they were blinded, or if we judged that the lack of blinding unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

We classified blinding as 'high risk of bias' if the blinding status of a trial was unclear or the trial was open.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we planned to re-include missing data in the analyses which we undertook.

We assessed the methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomization);
- unclear risk of bias.

We used a cut-off point of less than 20% of missing data to assess that a study is adequate.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);

- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);

- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we had about other possible sources of bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we planned to assess the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. In future updates, we will explore the impact of the level of bias through undertaking sensitivity analyses - see [Sensitivity analysis](#).

For this update, the quality of the evidence was re-assessed using the GRADE approach (Schunemann 2009) in order to assess the quality of the body of evidence relating to the following key outcomes for the main comparison between intervention (chlorhexidine vaginal wash) and control groups.

1. Chorioamnionitis
2. Postpartum endometritis
3. Neonatal sepsis
4. Blood culture confirming sepsis

The GRADEprofiler (GRADE 2008) was used to import data from Review Manager 5.3 (RevMan 2014) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes was produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

RESULTS

Description of studies

Results of the search

Two new studies (Pereira 2011; Saleem 2010) (both excluded) were identified from an updated search of the PCG Trials Register.

Included studies

We included three studies (Eriksen 1997; Rouse 1997; Rouse 2003) involving 3012 women in this review.

Eriksen 1997, from the USA, reported the effectiveness of chlorhexidine vaginal wash during labour to prevent neonatal infection. The data on peripartum infections of this study were reported in the other paper (Sweeten 1997). As they are both reports of the same trial we listed them under Eriksen 1997. Participants at 36 or more weeks' gestation in labour, excluding preterm labour, fetal distress, malpresentation, intra-amniotic infection, cervical dilatation greater than 6 cm and known allergy to chlorhexidine were eligible for the study. Informed consent was obtained from 1024 women who were eligible. Of these, 77 were excluded from the analysis because of incomplete records (71, 38 in the control and 33 in the study group); three participants were enrolled and subsequently discharged home; the vaginal wash was not given to two women; and there was one infant with anencephaly. Of the remaining 947 participants, 481 were randomized to the study arm and 466 served as controls. A computer software program was used to generate a random block allocation sequence to assign participants to either group. The randomization assignments were contained in sequentially numbered, opaque, sealed packets that were made up independent of the physicians managing the participants. The authors chose not to blind the study because the syringe containing chlorhexidine solution was pink and the investigators could not reproduce the colour artificially in the syringe containing the sterile water. For maternal outcomes, it is not very clear whether the intention-to-treat analysis was performed because it was not stated that 77 women were excluded before or after randomization. For neonatal outcomes, intention-to-treat analysis was not done because 24 neonatal charts in the chlorhexidine group and 13 in the control group were unavailable for review.

Rouse 1997, from the USA, reported a double-blinded clinical trial to determine whether chlorhexidine vaginal irrigation prevents maternal peripartal infection. Participants were eligible if they were admitted for delivery at or beyond 24 weeks' gestation. Exclusion criteria included a contra-indication for cervical digital examination, active genital herpes, chorioamnionitis and known or suspected allergy to chlorhexidine. The chlorhexidine and placebo bottles were randomly ordered with a computer-generated list and sequentially numbered with a peel-off study label. The active and placebo solutions were clinically indistinguishable. Among 3234 eligible participants, 1024 were randomized, 508 in chlorhexidine and 516 in placebo groups respectively. Because of incomplete or contradictory data, treatment allocation could not be determined for additional 10 women and these women were

not included in the analysis. Trial analysis was restricted to 1024 women and 1030 infants (six sets of twins).

[Rouse 2003](#), from the USA, reported a clinical trial of chlorhexidine vaginal irrigation to prevent peripartal infection in nulliparas. The study was conducted in two hospitals serving predominantly publicly funded patients. Women were eligible if they were nulliparous and admitted for delivery at or beyond 32 weeks' gestation. Exclusion criteria included a contra-indication to digital cervical examination, active genital herpes, chorioamnionitis and allergy to chlorhexidine. The chlorhexidine and placebo bottles were sequentially numbered (in groups of four) and randomly ordered based on a computer-generated list (one for each hospital). Each study bottle contained a peel-off label which, after use, was used to link participants to the correct study group. The chlorhexidine and placebo preparations were clinically indistinguishable. Four

women (two women in each group) were enrolled but actually did not undergo irrigation. They are included in the intention-to-treat analysis.

Excluded studies

We excluded five studies from an updated search in October 2010 ([Cutland 2009](#); [Mushangwe 2006](#); [Pereira 2006](#); [Saleem 2007](#); [Saleem 2010](#)) and two additional studies ([Pereira 2011](#); [Saleem 2010](#)) from the most recent updated search. In total, there are nine excluded studies. See the [Characteristics of excluded studies](#) table.

Risk of bias in included studies

See [Figure 1](#); [Figure 2](#) for a summary of all 'Risk of bias' assessments.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

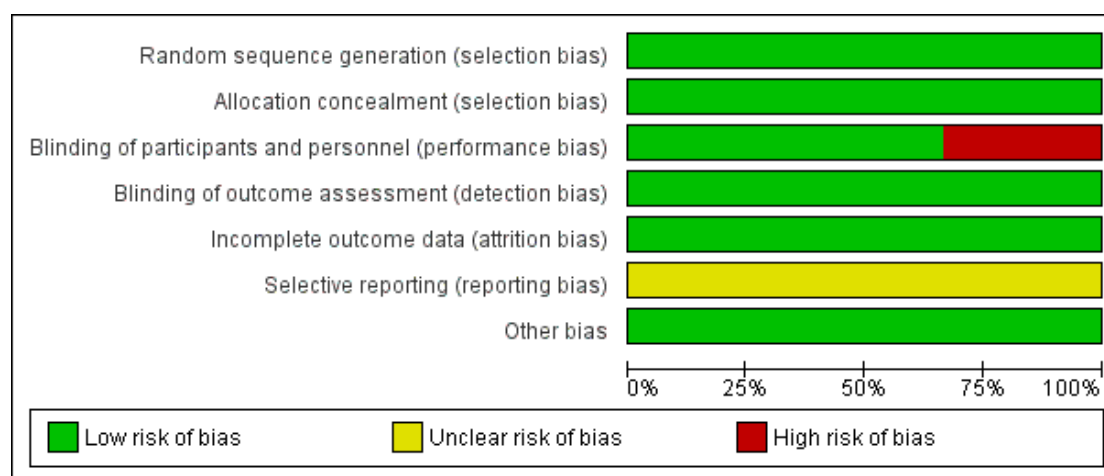


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Eriksen 1997							
Rouse 1997							
Rouse 2003							

Details for each trial are in the [Characteristics of included studies](#) table.

All included trials have a low risk of bias.

Allocation

All three included trials used computer-generated allocation sequences and used appropriate random allocation concealment.

Blinding

Two trials ([Rouse 1997](#); [Rouse 2003](#)) used indistinguishable placebo controls while one trial ([Eriksen 1997](#)) chose not to blind participants and personnel but the physicians managing infants in the nursery were unaware to which arm of the study each participant was randomized.

Incomplete outcome data

Two trials ([Rouse 1997](#); [Rouse 2003](#)) obtained the outcomes of all recruited mothers while the other ([Eriksen 1997](#)) excluded 7.5% (77/1024) and 11.1% (114/1024) of mothers and neonates from the analysis respectively.

Selective reporting

We did not have the protocols for all three trials and therefore could not evaluate selective reporting.

Other potential sources of bias

There were no other obvious potential sources of biases.

Effects of interventions

See: [Summary of findings for the main comparison Chlorhexidine vaginal wash versus placebo for preventing maternal and neonatal infections \(excluding Group B Streptococcal and HIV\)](#)

We included three studies involving 3012 women in this review.

Chlorhexidine vaginal wash versus placebo

Primary outcomes

Maternal outcomes

Three trials (3012 women) ([Eriksen 1997](#); [Rouse 1997](#); [Rouse 2003](#)) reported the incidence of chorioamnionitis, including 1514

and 1498 participants in the chlorhexidine and placebo groups respectively. There was no statistically significant difference between the two groups (risk ratio (RR) 1.10; 95% confidence interval (CI) 0.86 to 1.42) ([Analysis 1.1](#)). The same three trials also reported the incidence of postpartum endometritis. Although the data suggest a small reduction in the risk of postpartum endometritis with the use of the chlorhexidine vaginal wash, the difference was not statistically significant (RR 0.83; 95% CI 0.61 to 1.13) ([Analysis 1.2](#)).

Neonatal outcomes

Three trials (2987 infants) ([Eriksen 1997](#); [Rouse 1997](#); [Rouse 2003](#)) reported on neonatal outcomes, involving 1495 and 1492 neonates in the chlorhexidine and placebo groups respectively. For neonatal sepsis, which was evaluated in the three trials ([Eriksen 1997](#); [Rouse 1997](#); [Rouse 2003](#)) involving 1495 and 1492 neonates in the chlorhexidine and placebo groups respectively, there was no significant difference (RR 0.75; 95% CI 0.17 to 3.35) ([Analysis 1.7](#)).

Secondary outcomes

Maternal outcomes

There was no report about the other maternal outcomes and side effects of chlorhexidine in these three trials.

Neonatal outcomes

Two trials involving 1038 and 1039 (2077) neonates in the intervention and control groups respectively ([Rouse 1997](#); [Rouse 2003](#)) did not find significant difference in blood culture confirming sepsis (RR 0.75; 95% CI 0.17 to 3.35) ([Analysis 1.6](#)) and perinatal mortality (RR 1.00, 95% CI 0.17 to 5.79) (2071 infants, [Analysis 1.8](#)). One trial with 457 and 453 neonates in the intervention and control group respectively ([Eriksen 1997](#)), indicated that there was no significant difference in neonatal pneumonia (RR 0.33; 95% CI 0.01 to 8.09) (910 infants, [Analysis 1.4](#)). For neonatal meningitis, one trial with 508 and 516 neonates in the intervention and control groups respectively ([Rouse 1997](#)) did not show significant difference (RR 0.34; 95% CI 0.01 to 8.29) (1024 infants, [Analysis 1.5](#)). There was a trend that vaginal chlorhexidine during labour might lead to a higher tendency for newborns to receive antibiotics but this association is not statistically significant (RR 1.65; 95% CI 0.73 to 3.74) (one trial, 910 infants, [Analysis 1.9](#)). There was no report about the other neonatal outcomes and side effects of chlorhexidine in these three trials.

DISCUSSION

Although all three included trials are of high quality, one trial (Eriksen 1997) used only 20 mL of chlorhexidine or sterile water for vaginal irrigation, while the other two trials (Rouse 1997; Rouse 2003) used 200 mL of chlorhexidine or sterile saline solution. The effectiveness of vaginal chlorhexidine might also depend on the volume of the solution used for irrigation. Since chlorhexidine solution is quite safe, not expensive and vaginal irrigation is not difficult to perform, there is a need for a well-designed randomized controlled trial with adequate sample size to evaluate this simple intervention. However, the investigators of future trials must use the appropriate concentration and volume of vaginal chlorhexidine irrigation solution. We have identified two ongoing studies from the trial registration website www.clinicaltrials.gov (Madhi 2006; Moss 2006) since the review was first published.

Summary of main results

There was no evidence of an effect of vaginal chlorhexidine during labour in preventing maternal and neonatal infections.

Overall completeness and applicability of evidence

All three included studies were conducted in the USA. This limits the completeness and applicability of evidence to other parts of the world.

Quality of the evidence

All three included studies were of overall low risk of bias; however, only 3012 women were included in total. This review might not have enough power to detect small effect size. Assessment of the quality of the evidence using GRADE indicated that the levels of evidence for all primary outcomes and one important secondary outcome were low to moderate due to wide confidence interval crossing the line of no effect with few events ([Summary of findings for the main comparison](#)).

Potential biases in the review process

We carefully conducted this review following all steps recommended by the Cochrane Pregnancy and Childbirth Review Group. All review authors have no conflict of interest. There should not be any bias in the review process.

Agreements and disagreements with other studies or reviews

One Cochrane review (Stade 2008) has evaluated the effectiveness of vaginal chlorhexidine during labour for preventing early-onset group B streptococcal infection in newborn infants. Although there was a significant reduction in group B streptococcal colonization in neonates, there were no significant reductions in early-onset group B streptococcal sepsis, pneumonia, meningitis and mortality. One randomized controlled trial, involving 8011 women and their 8129 newborns, evaluated the effectiveness of chlorhexidine intravaginally and neonatal wipes for preventing early-onset neonatal sepsis (Cutland 2009). There was no significant reductions in either early-onset neonatal sepsis nor colonization of group B streptococcal. Another trial, involving 5008 women and their neonates, reported that chlorhexidine vaginal wipes during labour together with neonatal chlorhexidine wipes did not prevent neonatal sepsis, maternal and perinatal mortality (Saleem 2010).

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence to support the use of vaginal chlorhexidine douching during labour in preventing maternal and neonatal infections.

Implications for research

There is a need for a well-designed randomized controlled trial with appropriate concentration and volume of irrigation solution and adequate sample size.

ACKNOWLEDGEMENTS

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Khon Kaen University, Thailand and Thomas Jefferson University, USA.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Eriksen 1997

Methods	Randomized controlled trial, unblinded.
Participants	1024 term pregnant women presenting to labour and delivery. Included: 947 women (481 in chlorhexidine group (intervention) and 466 in sterile water group (control)) Excluded after randomization: 77 women (71 incomplete records, 3 discharged home, 2 vaginal wash was not given, 1 anencephalic)
Interventions	Vaginal wash with 20 mL of 0.4% chlorhexidine solution versus sterile water
Outcomes	Neonatal infection (pneumonia or sepsis) and use of antibiotics in neonates Periparturient infection (intra-amniotic infection and endometritis)
Notes	The report by Eriksen 1997 provided details of the neonatal outcomes. The report by Sweeten 1997 provided details of the maternal outcomes. This study was conducted in Houston, Texas, USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer software program (True Epistat, Richardson, TX) was used to generate a random block allocation sequence to assign women to either group
Allocation concealment (selection bias)	Low risk	The randomization assignments were contained in sequentially numbered, opaque, sealed packets that were made up independent of the physicians managing the women. The randomization was known only after the woman had been enrolled in the study
Blinding of participants and personnel (performance bias) All outcomes	High risk	The authors chose not to blind the study because the syringe containing the chlorhexidine solution was pink and "we could not reproduce the colour artificially in the syringe containing the sterile water"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Additionally, the physicians managing infants in the nursery were unaware to which arm of the study each participant was randomized

Eriksen 1997 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	1024 women were eligible for the study. Of these, 77 were excluded from the analysis for the following reasons: incomplete records (71), the patient was enrolled and subsequently discharged home (3), vaginal wash was not given (2), and a patient whose infant had anencephaly was inadvertently enrolled. Of the remaining 947 women, 481 were randomized to the study arm and 466 served as controls. 24 neonatal charts in the chlorhexidine group and 13 in the control group were unavailable for review. This left 457 neonates in the study group and 453 in a control group for analysis
Selective reporting (reporting bias)	Unclear risk	Protocol was not available for review.
Other bias	Low risk	No other obvious biases.

Rouse 1997

Methods	Double-blinded, placebo-controlled randomized clinical trial
Participants	1024 women (508 in the chlorhexidine group and 516 in the placebo group)
Interventions	Vaginal irrigation with 200 mL of 0.2% chlorhexidine or sterile water placebo
Outcomes	Peripartur infection (chorioamnionitis and endometritis (mutually exclusive) diagnosed) and neonatal infections
Notes	The study was conducted in Birmingham, Alabama, USA.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated.
Allocation concealment (selection bias)	Low risk	The chlorhexidine and placebo bottles were randomly ordered with a computer-generated list and sequentially numbered with peel-off study labels
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The active and placebo solutions were clinically indistinguishable

Rouse 1997 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	The active and placebo solutions were clinically indistinguishable
Incomplete outcome data (attrition bias) All outcomes	Low risk	A total of 1024 women were enrolled in the trial and underwent irrigation: 508 in the chlorhexidine group and 516 in the placebo group (Figure 1). Trial analysis was restricted to these 1024 women and their 1030 infants (6 sets of twins)
Selective reporting (reporting bias)	Unclear risk	Protocol was not available for review.
Other bias	Low risk	No other obvious biases.

Rouse 2003

Methods	Double-blinded, placebo-controlled randomized trial.
Participants	1041 women (525 in the chlorhexidine group and 516 in the placebo group)
Interventions	Vaginal irrigation with 200 mL of 0.2% chlorhexidine solution or sterile water every 6 hours during labour
Outcomes	Peripartur infection (chorioamnionitis and endometritis), neonatal sepsis and perinatal death
Notes	The study was conducted in Birmingham, Alabama, USA.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list (1 for each hospital).
Allocation concealment (selection bias)	Low risk	Both solutions were dispensed into sterile 225 mL flexible, high-density polyethylene bottles (W Braun, Miami, Fla), capped, and sealed. The chlorhexidine and placebo bottles were numbered sequentially (in groups of 4) and ordered randomly on the basis of a computer-generated list (1 for each hospital). The bottles were then placed into a study packet along with four sterile 12 cm douche nozzles (Massengill, SmithKline Beecham, Pittsburgh, Pa)

Rouse 2003 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Each study bottle contained a peel-off label which, after use was used to link participants to the correct study group. The chlorhexidine and placebo preparations were clinically indistinguishable
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Each study bottle contained a peel-off label which, after use, was used to link participants to the correct study group. The chlorhexidine and placebo preparations were clinically indistinguishable
Incomplete outcome data (attrition bias) All outcomes	Low risk	A total of 1041 women were enrolled in the trial: 525 women in the chlorhexidine group and 516 women in the placebo group. 4 women (2 women in each group) were enrolled but actually did not undergo irrigation. They are included in the intention-to-treat analysis
Selective reporting (reporting bias)	Unclear risk	Protocol was not available for review.
Other bias	Low risk	No other obvious biases.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Calkin 1996	The intervention in this study was vulva swabbing, not vaginal douching or washing during labour
Cutland 2009	This is a randomized placebo-controlled trial assessing the effect of vaginal and neonatal wipe with 0.6% chlorhexidine. The intervention of the study is not compatible with this intervention of interest in this review, which is vaginal douching only not including neonatal cleansing
Henrichsen 1994	Participants in the control group received chlorhexidine gel during vaginal exploration. Inadequate allocation concealment - randomization was performed by changing the regimen on a weekly basis, every Monday morning at 0800
Mushangwe 2006	Not a randomized controlled trial.
Pereira 2006	This is a randomized controlled trial to determine the safety and acceptability of 1% chlorhexidine vaginal washing of the vagina in labour and of the neonate after delivery. The intervention of the study is not compatible with this intervention of interest in this review, which is vaginal douching only not including neonatal cleansing

(Continued)

Pereira 2011	This is a randomized controlled trial conducted in Zimbabwe to determine the safety, acceptability, and antimicrobial effect of 1% chlorhexidine (CHX) vaginal washing of women in labour and their neonates. The intervention of the study is not compatible with the intervention of interest in this review, which is vaginal douching only not including neonatal cleansing
Saleem 2006	This is a randomized controlled trial to evaluate the feasibility of using vaginal/neonatal chlorhexidine (CHX) to reduce perinatal infections, morbidity and mortality in Pakistan. The intervention of the study is not compatible with the intervention of interest in this review, which is vaginal douching only not including neonatal cleansing
Saleem 2007	This is a randomized placebo-controlled trial assessing tolerance and safety of vaginal and neonatal wipe with 0.6% chlorhexidine. The intervention of the study is not compatible with the intervention of interest in this review, which is vaginal douching only not including neonatal cleansing
Saleem 2010	This is a randomized placebo-controlled trial assessing the effects of 0.6% chlorhexidine vaginal and baby wipes on fetal and neonatal mortality and infection-related morbidity. The intervention of the study is not compatible with the intervention of interest in this review, which is vaginal douching only, not including neonatal cleansing

Characteristics of ongoing studies [ordered by study ID]

Madhi 2006

Trial name or title	Preventing serious neonatal and maternal peripartum infections in developing country settings with a high prevalence of HIV infection: assessment of the disease burden and evaluation of an affordable intervention in Soweto, South Africa
Methods	
Participants	Healthy female volunteers aged 15 years and above. Expected enrolment: 8000
Interventions	0.5% chlorhexidine wipes of the birth canal during labour and of the infant at birth compared with external genitalia sterile water wipes
Outcomes	Primary outcomes: rates of culture-confirmed or clinical neonatal sepsis, < 3 days of life; rate of vertical transmission of colonization with group B streptococcus. Secondary outcomes: rates of culture-confirmed or clinical neonatal sepsis (non-nosocomial), 3 to 28 days of life; rates of serious maternal per partum infections including: endometritis, culture-confirmed postpartum sepsis, and postpartum perineal wound infection; rates of neonatal hospitalization, < 3 days of life; rates of neonatal hospitalization, < 28 days of life; rates of neonatal hospitalization, suspected sepsis; rate of vertical transmission of colonization with E. coli or Klebsiella species
Starting date	April 2004.
Contact information	Clare Cutland: +27 11 9899894; cutlandc@hivsa.com Shabir Madhi: +27 11 9899894; madhis@hivsa.com

Madhi 2006 (Continued)

Notes	Expected completion date: May 2008. ClinicalTrials.gov identifier NCT00136370

Moss 2006

Trial name or title	Randomized pilot trial of chlorhexidine vaginal and infant wash to reduce neonatal mortality
Methods	
Participants	Healthy female volunteers aged 16 years and above. Expected total enrolment: 1000. Setting: civil hospital in Karachi, Pakistan
Interventions	0.6% chlorhexidine solution every 4 hours until delivery (4 washes maximum) and 1 neonatal wash with the same solution compared with 200 mL of sterile physiologic saline solution
Outcomes	Primary outcomes: neonatal death or severe sepsis at 7 days. Secondary outcomes: maternal: clinical chorioamnionitis, clinical endometritis, urinary tract infection, sepsis, length of hospitalization, readmission to hospital, death; neonatals: receipt of antibiotics, duration of hospitalization, readmission to hospital
Starting date	June 2005.
Contact information	Nancy Moss: mossn@mail.nih.gov
Notes	Expected completion date: June 2006. ClinicalTrials.gov identifier NCT00121394

DATA AND ANALYSES

Comparison 1. Chlorhexidine vaginal wash versus placebo

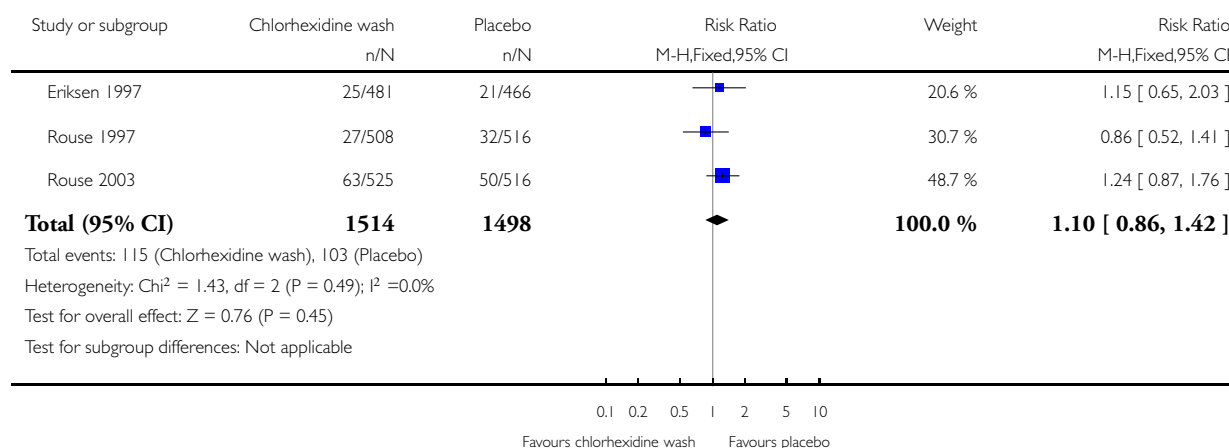
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Chorioamnionitis	3	3012	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.86, 1.42]
2 Postpartum endometritis	3	3012	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.61, 1.13]
3 Side effects	2	2065	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Neonatal pneumonia	1	910	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.09]
5 Neonatal meningitis	1	1024	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.29]
6 Blood culture confirming neonatal sepsis	2	2077	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.17, 3.35]
7 Neonatal sepsis	3	2987	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.17, 3.35]
8 Perinatal mortality	2	2071	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.17, 5.79]
9 Newborn received antibiotics	1	910	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [0.73, 3.74]

Analysis 1.1. Comparison 1 Chlorhexidine vaginal wash versus placebo, Outcome 1 Chorioamnionitis.

Review: Vaginal chlorhexidine during labour for preventing maternal and neonatal infections (excluding Group B Streptococcal and HIV)

Comparison: 1 Chlorhexidine vaginal wash versus placebo

Outcome: 1 Chorioamnionitis

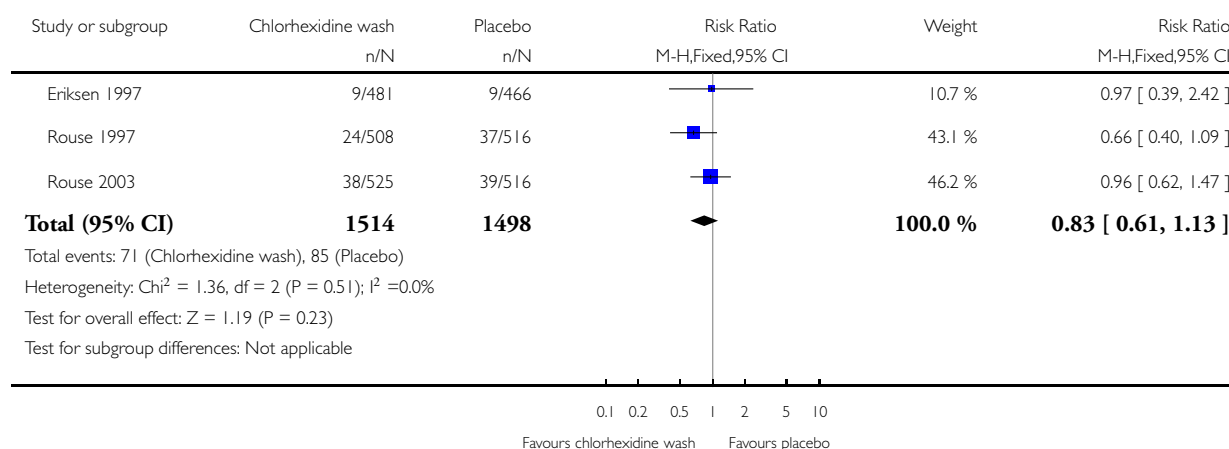


Analysis 1.2. Comparison 1 Chlorhexidine vaginal wash versus placebo, Outcome 2 Postpartum endometritis.

Review: Vaginal chlorhexidine during labour for preventing maternal and neonatal infections (excluding Group B Streptococcal and HIV)

Comparison: 1 Chlorhexidine vaginal wash versus placebo

Outcome: 2 Postpartum endometritis

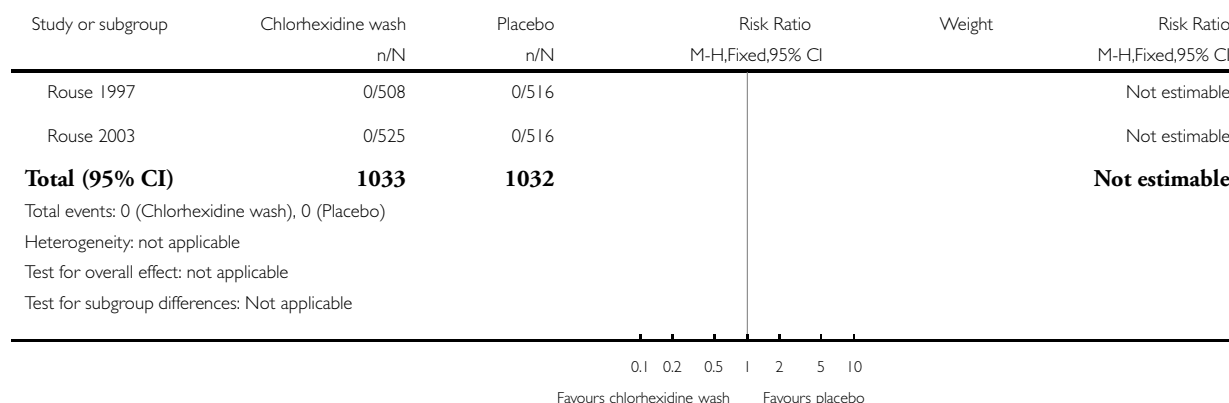


Analysis 1.3. Comparison 1 Chlorhexidine vaginal wash versus placebo, Outcome 3 Side effects.

Review: Vaginal chlorhexidine during labour for preventing maternal and neonatal infections (excluding Group B Streptococcal and HIV)

Comparison: 1 Chlorhexidine vaginal wash versus placebo

Outcome: 3 Side effects

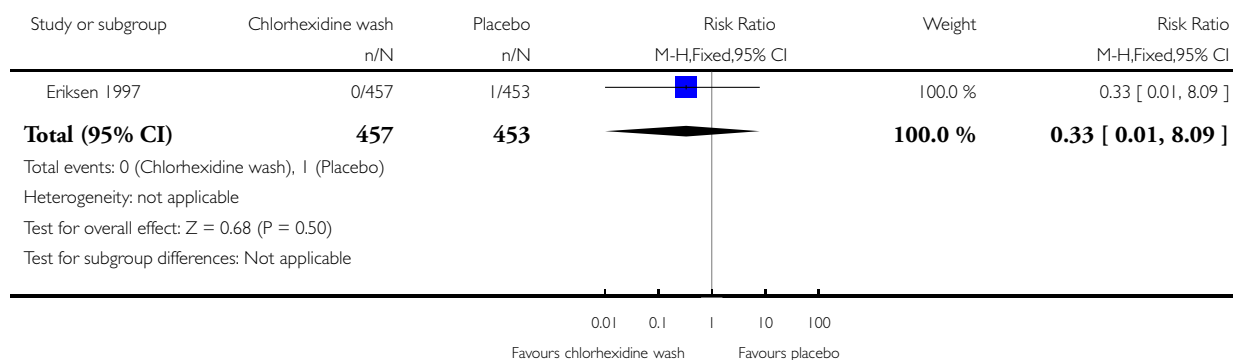


Analysis 1.4. Comparison 1 Chlorhexidine vaginal wash versus placebo, Outcome 4 Neonatal pneumonia.

Review: Vaginal chlorhexidine during labour for preventing maternal and neonatal infections (excluding Group B Streptococcal and HIV)

Comparison: 1 Chlorhexidine vaginal wash versus placebo

Outcome: 4 Neonatal pneumonia

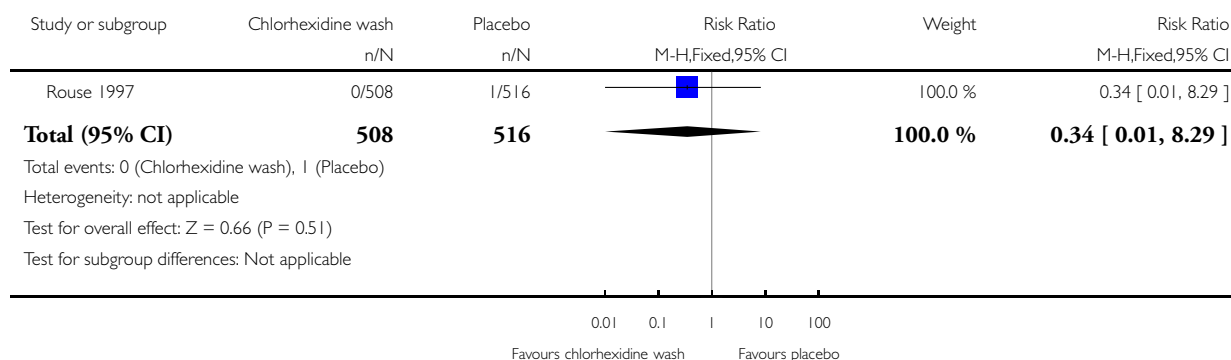


Analysis 1.5. Comparison 1 Chlorhexidine vaginal wash versus placebo, Outcome 5 Neonatal meningitis.

Review: Vaginal chlorhexidine during labour for preventing maternal and neonatal infections (excluding Group B Streptococcal and HIV)

Comparison: 1 Chlorhexidine vaginal wash versus placebo

Outcome: 5 Neonatal meningitis

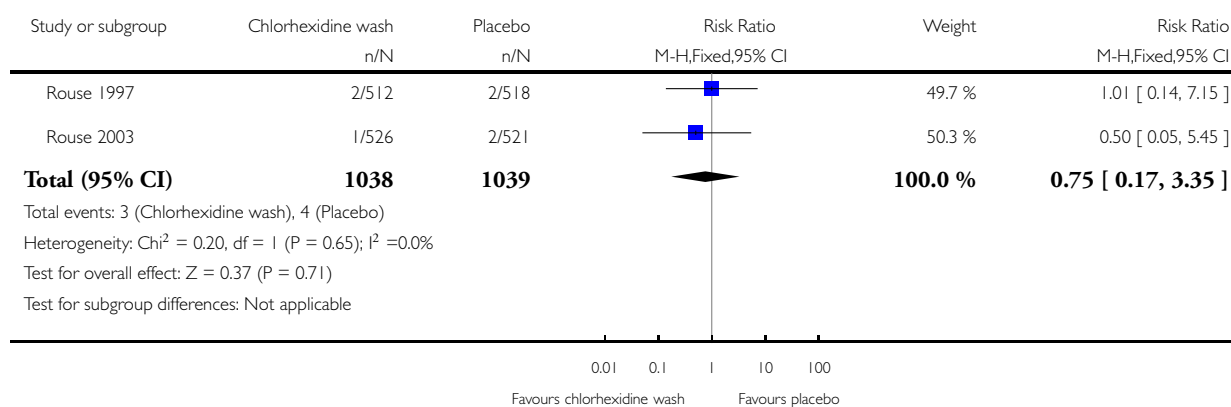


Analysis 1.6. Comparison 1 Chlorhexidine vaginal wash versus placebo, Outcome 6 Blood culture confirming neonatal sepsis.

Review: Vaginal chlorhexidine during labour for preventing maternal and neonatal infections (excluding Group B Streptococcal and HIV)

Comparison: 1 Chlorhexidine vaginal wash versus placebo

Outcome: 6 Blood culture confirming neonatal sepsis

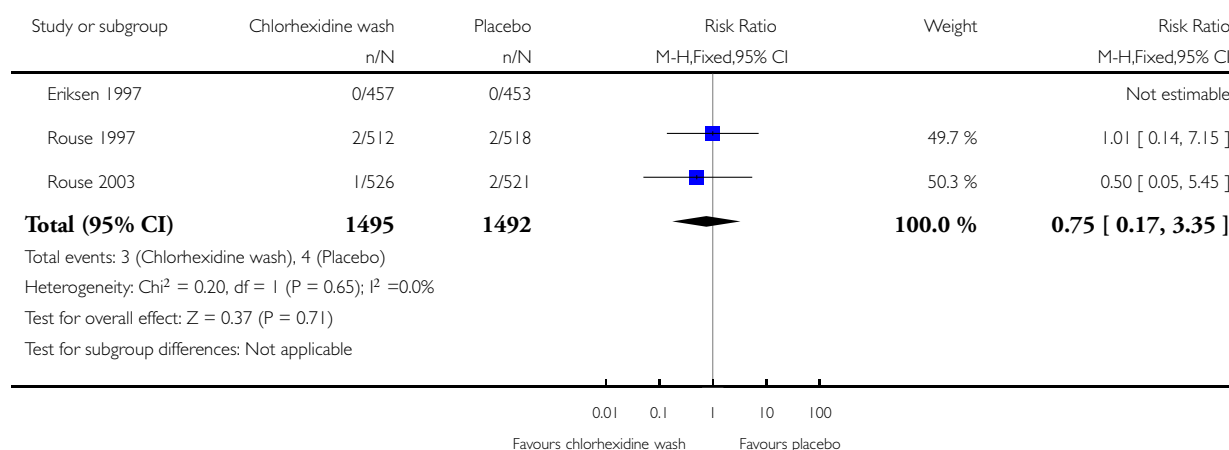


Analysis 1.7. Comparison 1 Chlorhexidine vaginal wash versus placebo, Outcome 7 Neonatal sepsis.

Review: Vaginal chlorhexidine during labour for preventing maternal and neonatal infections (excluding Group B Streptococcal and HIV)

Comparison: 1 Chlorhexidine vaginal wash versus placebo

Outcome: 7 Neonatal sepsis

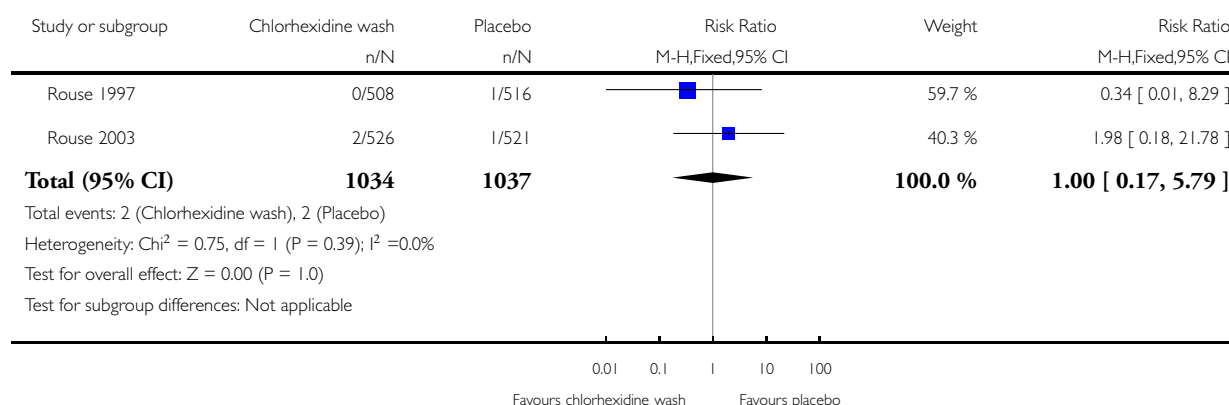


Analysis 1.8. Comparison 1 Chlorhexidine vaginal wash versus placebo, Outcome 8 Perinatal mortality.

Review: Vaginal chlorhexidine during labour for preventing maternal and neonatal infections (excluding Group B Streptococcal and HIV)

Comparison: 1 Chlorhexidine vaginal wash versus placebo

Outcome: 8 Perinatal mortality

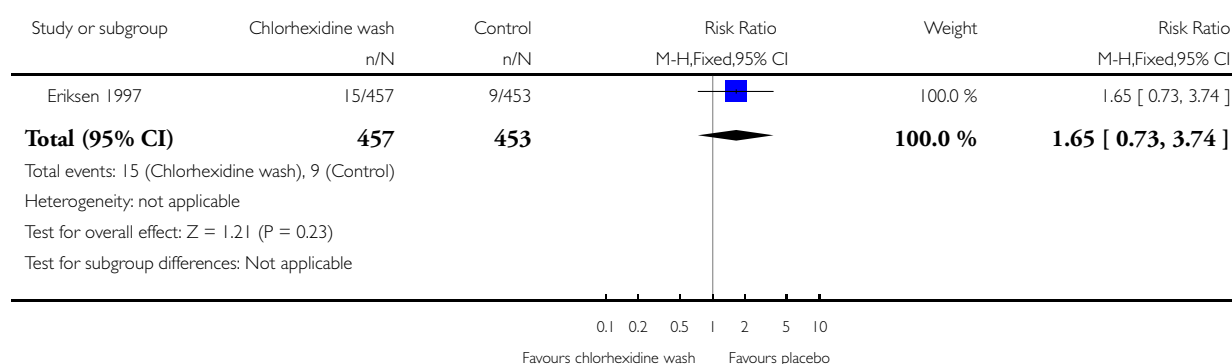


Analysis 1.9. Comparison 1 Chlorhexidine vaginal wash versus placebo, Outcome 9 Newborn received antibiotics.

Review: Vaginal chlorhexidine during labour for preventing maternal and neonatal infections (excluding Group B Streptococcal and HIV)

Comparison: 1 Chlorhexidine vaginal wash versus placebo

Outcome: 9 Newborn received antibiotics



APPENDICES

Appendix I. Search strategy for CENTRAL and MEDLINE

Authors searched the Cochrane Central Register of Controlled Trials (The Cochrane Library 2010, Issue 10), MEDLINE (from 1966 to 31 October 2010), LILACS (from 1982 to 31 October 2010) using the following keywords and free text terms: “chlorhexidine” or “vaginal-creams-foams-and-jellies” or “vaginal gel” or “vaginal wash” or “vaginal disinfection” and “peripartum” or “maternal” or “neonatal” or “labour” or “labor” or “infant-newborn”.

Appendix 2. Methods to be used in future updates

Data collection and analysis

Selection of studies

Two review authors will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult a third author.

We will create a study flow diagram to map out the number of records identified, included and excluded.

Data extraction and management

We will design a form to extract data. For eligible studies, at least two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult a third author. We will enter data into Review Manager software ([RevMan 2014](#)) and check for accuracy.

When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We will resolve any disagreement by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We will assess the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We will assess the methods as:

- low risk of bias (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.

We will assess methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomization);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We will assess the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We will describe for each included study any important concerns we have about other possible sources of bias.

We will assess whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Handbook* ([Higgins 2011](#)). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardized mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomized trials

We will include cluster-randomized trials in the analyses along with individually-randomized trials. We will adjust their sample sizes using the methods described in the *Handbook* [Section 16.3.4 or 16.3.6] using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomized trials and individually-randomized trials, we plan to synthesize the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomization unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomization unit and perform a sensitivity analysis to investigate the effects of the randomization unit.

Cross-over trials

We determined that it was not possible to include cross-over trials in this review.

Other unit of analysis issues

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomized to each group in the analyses, and all participants will be analyzed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomized minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the τ^2 , I^2 and χ^2 statistics. We will regard heterogeneity as substantial if an I^2 is greater than 30% and either a τ^2 is greater than zero, or there is a low P value (less than 0.10) in the χ^2 test for heterogeneity.

Assessment of reporting biases

If there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We will carry out statistical analysis using the Review Manager software ([RevMan 2014](#)). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average of the range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

If we use random-effects analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of τ^2 and I^2 .

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses for primary outcomes:

1. concentration of chlorhexidine (less than 0.4% versus 0.4% or higher);
2. volume of chlorhexidine solution (less than 200 mL versus 200 mL or more).

We will assess subgroup differences by interaction tests available within RevMan ([RevMan 2014](#)). We will report the results of subgroup analyses quoting the χ^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We plan to perform sensitivity analyses to explore the effect of study quality relating to the 'Risk of bias' items including allocation concealment, incomplete data collection to assess for any substantive difference to the overall result. If cluster-randomized trials are included in the review, we aim to apply other sensitivity analysis incorporating an estimate of the ICC taken from a different study, to see what the effect of different values of the ICC on the results of the analysis would be.

WHAT'S NEW

Last assessed as up-to-date: 30 June 2014.

Date	Event	Description
30 June 2014	New citation required but conclusions have not changed	Review updated.
30 June 2014	New search has been performed	Search updated. Two new trials identified and excluded (Pereira 2011 ; Saleem 2006).

HISTORY

Protocol first published: Issue 1, 2003

Review first published: Issue 4, 2004

Date	Event	Description
9 April 2011	New search has been performed	We reviewed five more studies from the updated search and excluded them all (Cutland 2009 ; Mushangwe 2006 ; Pereira 2006 ; Saleem 2007 ; Saleem 2010).
30 June 2009	Amended	Search updated. Three new reports identified.
20 September 2008	Amended	Converted to new review format.
27 April 2006	New search has been performed	We have identified two ongoing studies from the trial registration web site (Madhi 2006 ; Moss 2006) and another report for Rouse 2003 . There are no relevant data available yet.

CONTRIBUTIONS OF AUTHORS

Pisake Lumbiganon (PL) wrote the protocol. Jadsada Thinkhamrop (JT), Bandit Thinkhamrop (BT) and Jorge Tolosa (JET) commented on the early drafts and approved the published version. PL and JT conducted the review. BT assisted in the data analysis. PL drafted the review. JT, BT and JET gave significant intellectual comments on the review and approved the final version.

For the 2011 update, PL and JT independently reviewed five more studies from the updated search. PL drafted the updated review, which was then revised and approved by all review authors.

For the 2014 update, PL updated the search and PL and JT assessed the eligibility of the two studies identified from the updated search. PL created the 'Summary of findings' table using GRADEprofiler and drafted the text of the updated review, which was then revised and approved by all review authors.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Khon Kaen University, Thailand.
- Thomas Jefferson University, USA.

External sources

- UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research (RHR), World Health Organization, Switzerland.
- Thailand Research Fund, Distinguished Professor Award, Thailand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. Used Background sub-headings to structure the Background.
2. Categorized outcomes into primary and secondary outcomes.
3. Created a 'Summary of findings' table using GRADEprofiler.

NOTES

The ongoing reports identified through the updated search are preliminary reports of trials that may be relevant to this review. They will be assessed by the review team once the results of the main trials are available, at which time the review team will update this review.

INDEX TERMS

Medical Subject Headings (MeSH)

Labor, Obstetric; Anti-Infective Agents, Local [administration & dosage]; Bacterial Infections [* prevention & control]; Chlorhexidine [* administration & dosage]; Chorioamnionitis [prevention & control]; Endometritis [prevention & control]; Randomized Controlled Trials as Topic; Vaginal Douching [* methods]

MeSH check words

Adult; Female; Humans; Infant, Newborn; Pregnancy



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Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections (Review)

Siriwachirachai T, Sangkomkamhang US, Lumbiganon P, Laopaiboon M

Siriwachirachai T, Sangkomkamhang US, Lumbiganon P, Laopaiboon M.

Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections.

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	3
BACKGROUND	5
OBJECTIVES	6
METHODS	6
RESULTS	9
Figure 1.	10
Figure 2.	11
DISCUSSION	12
AUTHORS' CONCLUSIONS	12
ACKNOWLEDGEMENTS	12
REFERENCES	13
CHARACTERISTICS OF STUDIES	14
DATA AND ANALYSES	18
Analysis 1.1. Comparison 1 Antibiotic versus placebo, Outcome 1 Neonatal sepsis.	18
Analysis 1.2. Comparison 1 Antibiotic versus placebo, Outcome 2 Chorioamnionitis.	19
Analysis 1.3. Comparison 1 Antibiotic versus placebo, Outcome 3 Postpartum endometritis.	19
Analysis 1.4. Comparison 1 Antibiotic versus placebo, Outcome 4 Neonatal intensive care admissions.	20
WHAT'S NEW	20
HISTORY	20
CONTRIBUTIONS OF AUTHORS	21
DECLARATIONS OF INTEREST	21
SOURCES OF SUPPORT	21
INDEX TERMS	21

Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections

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ABSTRACT

Background

Chorioamnionitis is more likely to occur when meconium-stained amniotic fluid (MSAF) is present. Meconium may enhance the growth of bacteria in amniotic fluid by serving as a growth factor, inhibiting bacteriostatic properties of amniotic fluid. Many adverse neonatal outcomes related to MSAF result from meconium aspiration syndrome (MAS). MSAF is associated with both maternal and newborn infections. Antibiotics may be an effective option to reduce such morbidity.

Objectives

The objective of this review is to assess the efficacy and side effects of prophylactic antibiotics for MSAF during labour in preventing maternal and neonatal infections.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 September 2014).

Selection criteria

Randomised controlled trials (RCTs) comparing prophylactic antibiotics with placebo or no treatment during labour for women with MSAF.

Data collection and analysis

Two review authors independently assessed trials for inclusion and risk of bias, extracted data and checked them for accuracy.

Main results

We included two studies with 362 pregnant women. Both studies compared ampicillin-sulbactam (N = 183) versus normal saline (N = 179) in pregnant women with MSAF. Prophylactic antibiotics appeared to have no statistically significant reduction in the incidence of neonatal sepsis (risk ratio (RR) 1.00, 95% CI 0.21 to 4.76), neonatal intensive care unit (NICU) admission (RR 0.83, 95% CI 0.39 to 1.78) and postpartum endometritis (RR 0.50, 95% CI 0.18 to 1.38). However, there was a significant decrease in the risk of

chorioamnionitis (RR 0.36, 95% CI 0.21 to 0.62). No serious adverse effects were reported. Drug resistance, duration of mechanical ventilation and duration of admission to NICU/hospital were not reported. Most of the domains for risk of bias were at low risk of bias for one study and at unclear risk of bias for the other study. The quality of the evidence using GRADE was low for neonatal sepsis, postpartum endometritis, and neonatal mortality and morbidity prior to discharge (Neonatal intensive care admissions) and of moderate quality for chorioamnionitis.

Authors' conclusions

Current evidence indicates that compared to placebo, antibiotics for MSAF in labour may reduce chorioamnionitis. There was no evidence that antibiotics could reduce postpartum endometritis, neonatal sepsis and NICU admission. This systematic review identifies the need for more well-designed, adequately powered RCTs to assess the effect of prophylactic antibiotics in the incidence of maternal and neonatal complications.

PLAIN LANGUAGE SUMMARY

Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections

Meconium-stained amniotic fluid (MSAF) is the result of waste material from the fetal colon passing into the mother's amniotic cavity. Its incidence increases in post-term pregnancies. Pregnant women with MSAF are more likely to develop maternal complications including inflammation of the fetal membranes caused by a bacterial infection (chorioamnionitis), postpartum inflammation of the lining of the uterus (endometritis) and neonatal complications such as neonatal sepsis and the need for admission to a neonatal intensive care unit (NICU). Fetal stress or hypoxia may trigger gasping fetal respirations, which results in the aspiration of meconium.

Our review was based on two identified randomised controlled study (involving 362 women) and found that prophylactic antibiotics may reduce the risk of intra-amniotic infection in women with MSAF (*moderate quality evidence*). Antibiotics use did not clearly reduce neonatal sepsis (*low quality evidence*), NICU admission (*low quality evidence*) or postpartum endometritis (*low quality evidence*). Studies with much larger numbers of pregnant women with MSAF would be needed to examine these issues.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Antibiotic versus placebo for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections						
Population: Women with meconium-stained amniotic fluid in labour, gestational age more than 24 weeks						
Settings: A hospital, North Carolina, United States						
Intervention: Antibiotic versus placebo for preventing maternal and neonatal infections						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Antibiotic placebo versus				
Neonatal sepsis	Study population		RR 1 (0.21 to 4.76)	120 (1 study)	⊕⊕○○ low ¹	
	50 per 1000	50 per 1000 (10 to 238)				
	Moderate					
	50 per 1000	50 per 1000 (10 to 238)				
Chorioamnionitis	Study population		RR 0.36 (0.21 to 0.62)	362 (2 studies)	⊕⊕⊕○ moderate ²	
	240 per 1000	86 per 1000 (50 to 149)				
	Moderate					
	239 per 1000	86 per 1000 (50 to 148)				
Postpartum endometritis	Study population		RR 0.5 (0.18 to 1.38)	120 (1 study)	⊕⊕○○ low ¹	

	167 per 1000	83 per 1000 (30 to 230)			
	Moderate				
	167 per 1000	84 per 1000 (30 to 230)			
Mortality and morbidity prior to discharge (Neonatal intensive care admissions)	Study population		RR 0.83 (0.39 to 1.78)	120 (1 study)	⊕⊕○○ low ¹
	200 per 1000	166 per 1000 (78 to 356)			
	Moderate				
	200 per 1000	166 per 1000 (78 to 356)			
Side effects of treatment	Not estimable		0 (0 study)	See comment	This outcome was not reported in any of the included studies
Duration of admission to neonatal intensive care unit	Not estimable		0 (0 study)	See comment	This outcome was not reported in any of the included studies
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio;					
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.					

¹ Wide confidence interval crossing the line of no effect, small sample size and few events (-2).

² Most weight contributed by a study with design limitations (-1).

BACKGROUND

Description of the condition

Meconium-stained amniotic fluid (MSAF), as a result of the passage of fetal colonic contents into the amniotic cavity, occurs in approximately 12% of all deliveries (Cleary 1998). The incidence of intrapartum MSAF ranges from 7% to 22% for a term pregnancy but this figure increases to up to 40% in a post-term pregnancy (Katz 1992). The composition of meconium from a term fetus is primarily water (70% to 80%). Other constituents include mucopolysaccharides, cholesterol and its precursors, proteins, lipids, bile acids and salts (giving the characteristic green colour), pancreatic enzymes, interleukin-8, phospholipase A2, squamous cells, and vernix caseosa (white substance coating the skin of newborn babies) (Cleary 1998; Usta 2000).

MSAF may act directly and indirectly on exposed tissue. Its effects depend on the concentration of meconium, duration of exposure, and the presence of associated stress factors (hypoxia, infection). MSAF has long been associated with potentially adverse fetal outcomes including meconium aspiration syndrome (MAS), admission to neonatal intensive care unit (NICU), neonatal sepsis, cerebral palsy, seizure and pulmonary diseases (Berkus 1994; Katz 1992; Nathan 1994). Many adverse neonatal outcomes related to MSAF result from MAS. MAS occurs in 5% of the cases of MSAF and more than 4% of infants with MAS die, accounting for 2% of all perinatal deaths (Cleary 1998; Wiswell 1990). Hypoxia is the key factor that triggers gasping fetal respirations, which results in the aspiration of meconium. Most cases of MAS probably result from in utero aspiration rather than aspiration at the time of delivery. In addition to possibly contributing to respiratory distress in the neonate, MSAF has been associated with a higher risk of neonatal infection (Romero 1991). Chorioamnionitis is a risk factor for neonatal sepsis, which results in NICU admissions and potential fetal morbidity and death (Alexander 1999). Fetal microbial invasion has been proposed to cause inflammatory brain damage through the effects of elevated cytokines (e.g. tumour necrosis factor (TNF) alpha, IL-1 beta, and IL-6) (Hoskins 1987).

Chorioamnionitis is also more likely to occur when MSAF is present (Mazor 1995; Romero 1991; Usta 2000). The risk of clinical chorioamnionitis and histological chorioamnionitis in patients with intrapartum MSAF is significantly higher than those with clear fluid. The risk for clinically diagnosed endometritis is two-fold (Markovitch 1993; Mazor 1995). Intrapartum chorioamnionitis is associated with dystocia and increased risk for operative delivery (Casey 1997; Mark 2000). Unrecognised or undertreated chorioamnionitis can lead to postpartum endomyometritis, which can result in further maternal morbidity, and increased length of stay in hospital and hospital costs. MSAF is the risk factor for microbial invasion of the amniotic cavity in patients with intact membranes and preterm labour (Romero 1991). Maternal infection is also more likely in the presence of MSAF. Pa-

tients with MSAF were almost two and a half times as likely to develop postoperative endometritis (Josephson 1984). There are statistically significant associations between MSAF and puerperal infection in term deliveries (Piper 1998). Puerperal infection rates are associated with the degree of meconium staining, with rates rising as meconium thickness increases (Tran 2003). There is a three-fold increase in positive amniotic fluid cultures in patients with MSAF compared to those with clear amniotic fluid (Mazor 1995; Romero 1991). The most common amniotic fluid isolates in MSAF are anaerobes, *Ureaplasma urealyticum*, *Streptococci*, *Escherichia coli*, *Candida albicans* and *Listeria monocytogenes* (Mazor 1995; Romero 1991).

Meconium may enhance the growth of bacteria in amniotic fluid by serving as a growth factor, inhibiting bacteriostatic properties of amniotic fluid, or antagonising host defence systems, thus increasing the risk of chorioamnionitis. Generally, amniotic fluid is a poor culture medium for *Escherichia coli*, *Listeria monocytogenes* and *Staphylococcus aureus*; however, with enough meconium, amniotic fluid becomes an excellent culture medium (Florman 1969). Meconium may alter the zinc-to-phosphorous ratio in amniotic fluid and facilitate bacterial growth and decrease host defences (Hoskins 1987). Light and very light MSAF significantly impair mechanisms for intracellular microbial killing. The phagocytic ability of neutrophils (a type of white blood cell) was also significantly diminished in the presence of moderate MSAF (Clark 1995). Mechanisms of meconium-associated puerperal infections include altering the antibacterial properties of amniotic fluid and enhancing bacterial growth, impairing the host immune response through the inhibition of phagocytosis and neutrophil oxidative burst (Clark 1995; Katz 1992).

Description of the intervention

One study has shown a significant reduction in the rate of clinical chorioamnionitis when the intervention ampicillin-sulbactam was administered prophylactically for the indication of MSAF (Edwards 1999).

How the intervention might work

Antibiotics can be bacteriostatic (they stop bacteria from multiplying) or bactericidal (they kill the bacteria). To perform either of these functions, antibiotics must be brought into contact with the bacteria. Antibiotics are thought to interfere with the surfactant of bacteria cells, causing a change in their ability to reproduce (Heizmann 2007). Gentamicin is an aminoglycoside antibiotic with bactericidal activity that acts at the 30S bacterial ribosomal subunit, inhibiting the synthesis of bacterial proteins (Ward 2008).

Why it is important to do this review

Cochrane reviews have addressed a number of issues about MAS including steroid therapy, endotracheal intubation, surfactant and antibiotics for neonates (Halliday 2001; Shivananda 2006; Ward 2003). Other interventions include amnioinfusion for MSAF in labour (Hofmeyr 2014). Prophylactic intravenous intrapartum ampicillin-sulbactam therapy or cefazolin infusion into the amniotic cavity during amnioinfusion in mothers with MSAF did not show any benefit in reducing chorioamnionitis, endometritis and neonatal sepsis (Adair 1996; Edwards 1999). However, the role of antibiotics for MSAF during labour has not been systematically evaluated.

OBJECTIVES

The objective of this review is to assess the efficacy and side effects of prophylactic antibiotics for meconium-stained amniotic fluid during labour in preventing maternal and neonatal infections.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) of prophylactic antibiotic administration during labour for women with MSAF. We excluded quasi-RCTs. Conference abstracts were considered eligible for inclusion.

Types of participants

Pregnant women with a gestational age of more than 22 weeks who were in labour and had MSAF.

Types of interventions

Systemic prophylactic antibiotics started during labour in women with MSAF compared with no treatment or placebo.

Types of outcome measures

The primary outcomes were the most clinically important for the neonate, whereas the secondary outcomes also included maternal and neonatal complications.

Primary outcomes

1. Neonatal sepsis.
(Definition of sepsis as defined by authors.)

Secondary outcomes

Maternal

1. Intrapartum chorioamnionitis.
2. Postpartum endometritis.
3. Side effects of treatment, e.g. drug allergy, anaphylactic shock.
4. Drug resistance.

Neonatal

1. Mortality and morbidity prior to discharge, e.g. birth asphyxia, intracranial haemorrhage, intraventricular haemorrhage, necrotising enterocolitis and admission to neonatal intensive care unit (NICU).
2. Duration of mechanical ventilation (days).
3. Duration of admission to NICU/hospital.

Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (30 September 2014).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
 2. weekly searches of MEDLINE;
 3. weekly searches of Embase;
 4. handsearches of 30 journals and the proceedings of major conferences;
 5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.
- Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).
- Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search

Co-ordinator searches the register for each review using the topic list rather than keywords.
We did not apply any language restrictions.

Data collection and analysis

For methods used in the previous version of this review, please refer to [Siriwachirachai 2010](#).

For this update (2014), the following methods were used for full 'Risk of bias' assessment and assessment of the quality of evidence using the GRADE approach.

Selection of studies

Thitiporn Siriwachirachai (TS) and Ussanee Sangkomkarnhang (US) independently assessed trials for inclusion and methodological quality. There were no disagreements.

Data extraction and management

We designed a form to extract data. For eligible studies, TS and US independently extracted the data using the agreed form. There were no discrepancies. We entered the data into Review Manager software ([RevMan 2014](#)) and checked for accuracy. We did not contact the original study authors because the reported information was sufficient in the report.

Assessment of risk of bias in included studies

TS and US independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

(1) Random sequence generation (checking for possible selection bias)

We described for the one included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for the included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for the included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that the study would be at low risk of bias if they were blinded, or if we judged that the lack of blinding unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for the included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for the included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we planned to re-include missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for the included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for the included study any important concerns we had about other possible sources of bias.

(7) Overall risk of bias

We made explicit judgements about whether the one included study was at high risk of bias, according to the criteria given in the *Cochrane Handbook of Reviews of Intervention* (Higgins 2011). With reference to (1) to (6) above, we planned to assess the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. In future updates, we will explore the impact of the level of bias through undertaking sensitivity analyses - see [Sensitivity analysis](#).

For this update the quality of the evidence was assessed using the GRADE approach (Schunemann 2009) in order to assess the quality of the body of evidence relating to the following the outcomes.

1. Neonatal sepsis
2. Intrapartum chorioamnionitis.
3. Postpartum endometritis.
4. Side effects of treatment, e.g. drug allergy, anaphylactic shock.
5. Mortality and morbidity prior to discharge, e.g. birth asphyxia, intracranial haemorrhage, intraventricular haemorrhage, necrotising enterocolitis and admission to NICU.
6. Duration of admission to NICU/hospital.

Although, we could not assess some outcomes listed due to lack of data, we were able to assess neonatal sepsis, chorioamnionitis, and postpartum endometritis.

GRADE profiler (GRADE 2008) was used to import data from Review Manager 5.3 (RevMan 2014) in order to create 'Summary of findings' tables. In future updates, if more studies are included a summary of the intervention effect and a measure of quality for each of the above outcomes will be produced using the GRADE approach.

The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratios (RR) with 95% confidence intervals (CIs).

Continuous data

For continuous data, we planned to use the mean difference if outcomes were measured in the same way between trials. We planned to use the standardised mean difference to combine trials that measure the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomised trials

We included only one randomised controlled trial (RCT). In future updates, if we identify cluster-randomised trials, we will include these in the analyses along with individually-randomised trials. We will adjust their sample sizes using the methods described in the *Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population (Higgins 2009). If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and we consider the interaction between the effect of intervention and the choice of randomisation unit to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a subgroup analysis to investigate the effects of the randomisation unit.

Dealing with missing data

For the included study, we noted levels of attrition. We planned to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis; i.e. we attempted to include all participants randomised to each group in the analyses, and analysed all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in the included trial is the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

This review did not include meta-analysis. In future updates, as more data become available, we will assess statistical heterogeneity in each meta-analysis using the τ^2 , I^2 and χ^2 statistics. We will regard heterogeneity as substantial if a τ^2 is greater than zero and either an I^2 is greater than 30% or there is a low P value (less than 0.10) in the χ^2 test for heterogeneity.

Assessment of reporting biases

In subsequent updates of this review, if there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014). This review only included one RCT so we did not pool any data. In future updates, if more data become available, we will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary if an average treatment effect across trials is considered clinically meaningful. We will treat the random-effects summary as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

If we use random-effects analyses, we will present the results as the average treatment effect with its 95% confidence interval, and the estimates of τ^2 and I^2 .

Subgroup analysis and investigation of heterogeneity

In future updates of this review, when sufficient data become available, we plan to carry out the following subgroup analyses:

1. intact versus rupture membrane;
2. single versus combine antibiotic regimens;
3. duration of antibiotics less than 24 hours versus more than 24 hours.

We will use the following outcomes in subgroup analysis:

- early onset neonatal sepsis (symptomatic before 72 hours of age);
- late onset neonatal sepsis (symptomatic after 72 hours of age).

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2014). We will report the results of subgroup analyses quoting the χ^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

In subsequent updates we also plan to conduct a sensitivity analysis to compare the results using all studies and using only those of high methodological quality, i.e. comparing studies at low risk of bias versus high risk of bias.

RESULTS

Description of studies

Results of the search

We identified four publications as potentially eligible for inclusion in this review.

Included studies

This review includes two RCT (Adair 1996; Adair 1999) in which 362 women were randomised and the results analysed; see [Characteristics of included studies](#).

Excluded studies

We assessed and excluded two retrospective cohort studies (Adair 1998; Edwards 1999); see [Characteristics of excluded studies](#).

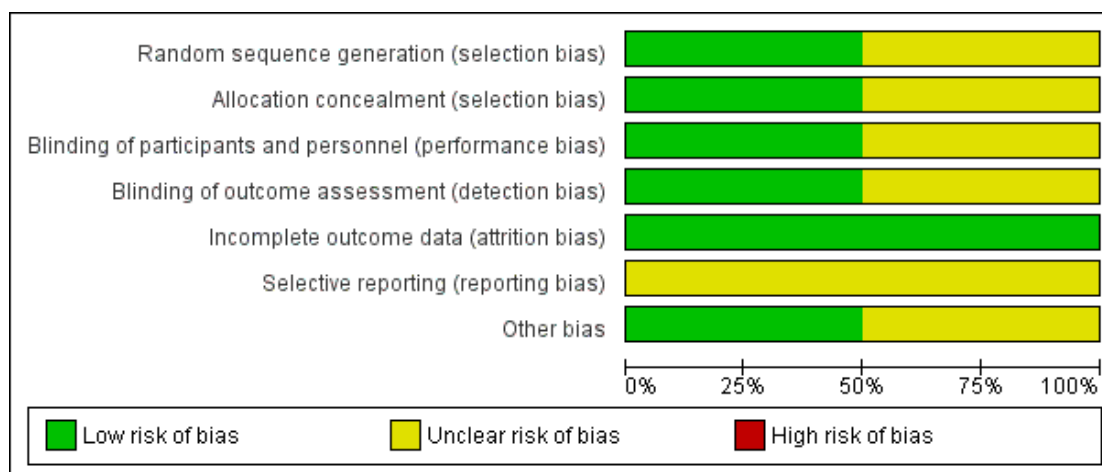
Risk of bias in included studies

We have summarised the risk of bias of the included studies (Adair 1996; Adair 1999) in [Figure 1](#) and [Figure 2](#).

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Adair 1996	+	+	+	+	+	?	+
Adair 1999	?	?	?	?	+	?	?

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Allocation

One trial reported clear information on allocation concealment. The randomisation schedule was generated and kept in an area away from the clinical area and was unavailable to caregivers (Adair 1996). Another trial, published as a conference abstract contained little information and so it was unclear how randomisation and allocation concealment had been performed (Adair 1999).

Blinding

Adair 1996 reported participants and all caregivers were thoroughly blinded until the study was completed. Interventions were identically prepared in 100 mL fluid bags and issued by one of two research nurses, independent to the trial investigators. The outcome assessors were also blinded to the randomisation status. The other trial report did not contain enough information to be able tell whether blinding had been undertaken (Adair 1999).

Incomplete outcome data

Two trials (Adair 1996; Adair 1999) reported no withdrawals. Adair 1996 reported analysis based on intention-to-treat basis.

Selective reporting

We do not have access to this study protocol; therefore we could not evaluate this risk of bias.

Other potential sources of bias

None apparent in one study (Adair 1996); and unclear in the other study published in abstract form (Adair 1999).

Effects of interventions

See: [Summary of findings for the main comparison Antibiotic versus placebo for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections](#)

Results are based on two randomized controlled trials (362 women).

Antibiotic versus placebo

Primary outcomes

There was no significant reduction in the incidence of neonatal sepsis (risk ratio (RR) 1.00, 95% confidence interval (CI) 0.21 to 4.76; one study; 120 women), see [Analysis 1.1](#). Adair 1996 did not report their results in terms of early and late onset neonatal sepsis.

Secondary outcomes

There was a significant reduction in the incidence of chorioamnionitis in the ampicillin-sulbactam group compared with placebo (RR 0.36, 95% CI 0.21 to 0.62; two studies; 362 women), see [Analysis 1.2](#). There was no significant reduction in the incidence of endometritis (RR 0.50, 95% CI 0.18 to 1.38; one study; 120 women), see [Analysis 1.3](#) or neonatal intensive care unit (NICU) admission (RR 0.83, 95% CI 0.39 to 1.78; one study; 120 women), see [Analysis 1.4](#).

No serious adverse effects were reported. Drug resistance, duration of mechanical ventilation and duration of admission to NICU/hospital were not reported

DISCUSSION

Summary of main results

There was a significant reduction in the incidence of chorioamnionitis in mothers who received ampicillin-sulbactam compared to placebo. Neonatal sepsis was not differentiated into 'early' or 'late' onset but there was no difference in the incidence of neonatal sepsis between the two groups. Endometritis was not statistically reduced. There was no information about adverse effects.

Overall completeness and applicability of evidence

Two randomised controlled trials (RCT) from a developed country were included in this review and they did not report the primary outcome 'neonatal sepsis' in terms of early or late onset. The evidence may be insufficient to evaluate the efficacy and side effects of prophylactic antibiotics for meconium-stained amniotic fluid in labour for preventing neonatal sepsis.

Quality of the evidence

Most of the domains for risk of bias were at low risk of bias for one study (Adair 1996) and at unclear risk of bias for the other study (Adair 1999). The quality of the evidence using GRADE was low for neonatal sepsis, postpartum endometritis, and neonatal mortality and morbidity prior to discharge (Neonatal intensive care admissions) and of moderate quality for chorioamnionitis. No serious adverse effects were reported. Drug resistance, duration of mechanical ventilation and duration of admission to NICU/hospital were not reported.

Potential biases in the review process

We followed the process of review as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* Higgins 2009. We

also did an exhaustive search which included many clinical trial registries.

Agreements and disagreements with other studies or reviews

There are no other reviews and studies related to the efficacy and side effects of prophylactic antibiotics for MSAF during labour in preventing maternal and neonatal infections.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to support the use of prophylactic antibiotics in women with meconium-stained amniotic fluid (MSAF) during labour because the rates of neonatal sepsis were not different in the two groups.

Implications for research

This systematic review has identified the need for more well-designed, adequately powered RCTs to assess the benefits and harms of antibiotic prophylactic in MSAF during labour for preventing neonatal sepsis. The trials should include clinical outcomes of neonatal sepsis for both early onset neonatal sepsis (symptomatic before 72 hours of age) and late onset neonatal sepsis (symptomatic after 72 hours of age).

ACKNOWLEDGEMENTS

As part of the pre-publication editorial process, this review has been commented on by two peers (an editor and referee who is external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser. We thank Erika Ota and Nancy Medley for help in preparing the 'Summary of findings' table.

Erika Ota and Nancy Medley's work was financially supported by the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research (RHR), World Health Organization. The named authors alone are responsible for the views expressed in this publication.

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- * Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Adair 1996

Methods	Randomised trial with allocation concealment using computer-generated randomisation list. All participants, caregivers and outcome assessors were blinded to the treatment regimen	
Participants	Intervention group: 60 pregnant women (mean age 24.5, SD 6.3) with gestational age more than 24 weeks (mean 39.8, SD 1.0) Control group: 60 pregnant women (mean age 25.9, SD 6.3), (mean gestational age 39.9, SD 1.2) Inclusion criteria: gestational age more than 24 weeks with MSAF complicating the intrapartum Exclusion criteria: women with penicillin and/or cephalosporin allergy, evidence of active infection, presence of intrauterine death, GA < 24 weeks, or history of antibiotics use in 7 days Location: North Carolina, United States.	
Interventions	Intervention: ampicillin-sulbactam 3.0 g intravenous prepared in 100 mL fluid bags, and was repeated every 6 hours until delivery Control: normal saline infused as an IV bolus.	
Outcomes	Mother Chorioamnionitis. Postpartum endometritis. Neonatal Number of NICU admissions. Incidence of sepsis (not defined), and adverse outcomes including enterocolitis and respiratory distress	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using a computer-generated list.
Allocation concealment (selection bias)	Low risk	Adequate: there was randomisation by computer-generated list and both IV preparations were prepared by 1 of 2 research nurses who were not involved in this study

Adair 1996 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Adequate: ampicillin-sulbactam and normal saline were identically prepared. Both preparations were prepared by research nurses who were not involved in the clinical care of the women
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Adequate: all caregivers were blinded to the randomisation status of the woman
Incomplete outcome data (attrition bias) All outcomes	Low risk	Adequate: there were no withdrawals.
Selective reporting (reporting bias)	Unclear risk	Unclear, because we do not have access to this trial's protocol
Other bias	Low risk	Study appeared to be free of other sources of bias.

Adair 1999

Methods	No information of randomisation, allocation concealment and blinding	
Participants	Intervention group: 123 pregnant women (mean age 24.8, SD 3.7), (mean gestational age 39.8, SD 1.9) with intrapartum diagnosis of MSAF Control group: 119 pregnant women (mean age 23.4, SD 3.4), (mean gestational age 39.8, SD 1.1) with intrapartum diagnosis of MSAF Inclusion criteria: absence of obvious infection, temperature < 100 F, MSAF passage and willingness to participate Exclusion criteria: fetal heart rate > 180, penicillin or cephalosporin allergy	
Interventions	Intervention: ampicillin-sulbactam 3.0 g intravenous. Control: normal saline.	
Outcomes	Intra- amniotic infection.	
Notes	Data from conference abstract.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.

Adair 1999 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss of follow up.
Selective reporting (reporting bias)	Unclear risk	Not described.
Other bias	Unclear risk	Not described.

GA: gestational age

IV: intravenous

MSAF: meconium-stained amniotic fluid

NICU: neonatal intensive care unit

RCT: randomised controlled trial

SD: standard deviation

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Adair 1998	Not a RCT, this was a retrospective cohort study.
Edwards 1999	Intervention not of interest to systematic review; not systematic prophylactic antibiotics

RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Antibiotic versus placebo

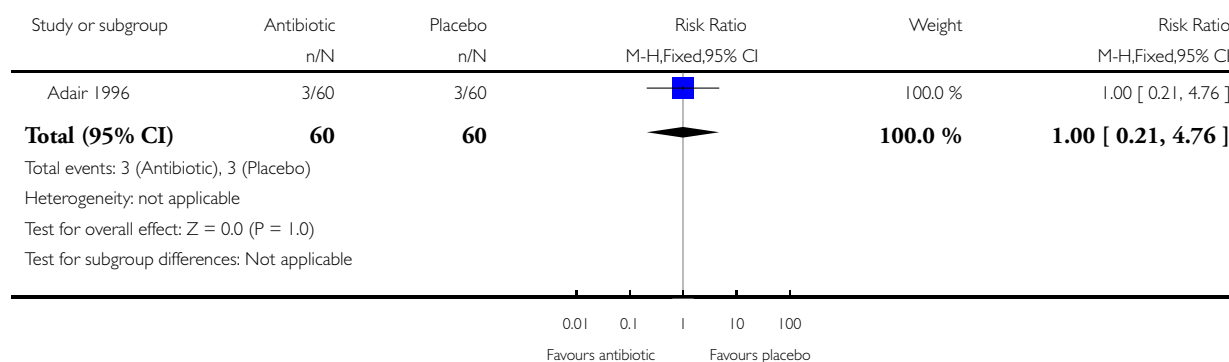
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neonatal sepsis	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.21, 4.76]
2 Chorioamnionitis	2	362	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.21, 0.62]
3 Postpartum endometritis	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.18, 1.38]
4 Neonatal intensive care admissions	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.39, 1.78]

Analysis 1.1. Comparison 1 Antibiotic versus placebo, Outcome 1 Neonatal sepsis.

Review: Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections

Comparison: 1 Antibiotic versus placebo

Outcome: 1 Neonatal sepsis

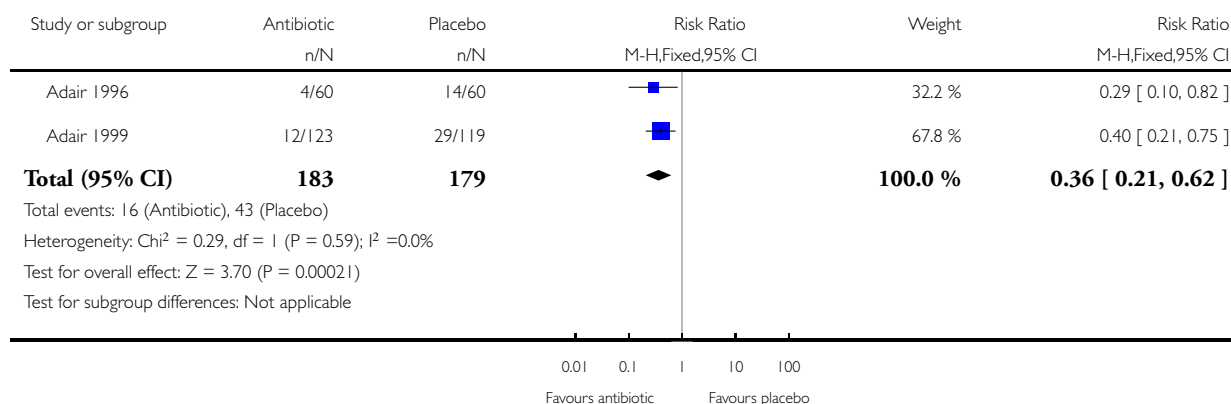


Analysis 1.2. Comparison 1 Antibiotic versus placebo, Outcome 2 Chorioamnionitis.

Review: Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections

Comparison: 1 Antibiotic versus placebo

Outcome: 2 Chorioamnionitis

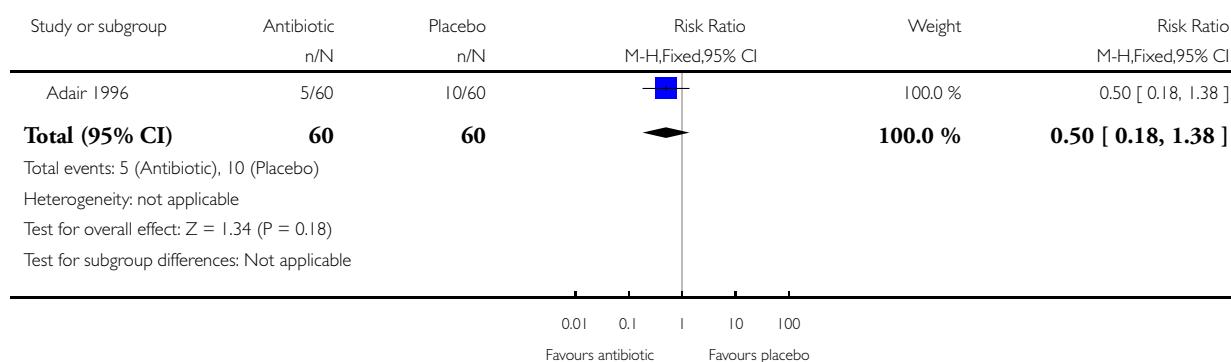


Analysis 1.3. Comparison 1 Antibiotic versus placebo, Outcome 3 Postpartum endometritis.

Review: Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections

Comparison: 1 Antibiotic versus placebo

Outcome: 3 Postpartum endometritis

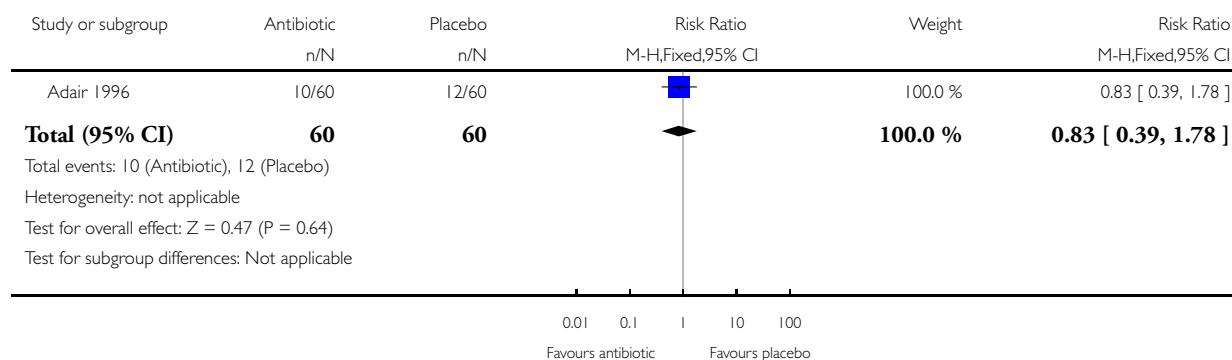


Analysis 1.4. Comparison 1 Antibiotic versus placebo, Outcome 4 Neonatal intensive care admissions.

Review: Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections

Comparison: 1 Antibiotic versus placebo

Outcome: 4 Neonatal intensive care admissions



WHAT'S NEW

Last assessed as up-to-date: 30 September 2014.

Date	Event	Description
30 September 2014	New citation required but conclusions have not changed	Review updated.
30 September 2014	New search has been performed	Updated search and methods. No new trials identified. 'Summary of findings' table incorporated. One previously excluded study (Adair 1999) is now included.

HISTORY

Protocol first published: Issue 2, 2009

Review first published: Issue 12, 2010

Date	Event	Description
18 January 2012	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

Thitiporn Siriwachirachai and Ussanee Sangkomkamhang drafted the review, Pisake Lumbiganon and Malinee Laopaiboon revised and approved the final version of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Khon Kaen Hospital, Ministry of Public Health, Thailand.
- Faculty of Medicine, Khon Kaen University, Thailand.
- Faculty of Public Health, Khon Kaen University, Thailand.

External sources

- Thailand Research Fund, Senior Research Scholar, Thailand.
- Thai Cochrane Network, Thailand.
- UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research (RHR), World Health Organization, Switzerland.

INDEX TERMS

Medical Subject Headings (MeSH)

*Amniotic Fluid; *Labor, Obstetric; *Meconium; Ampicillin [therapeutic use]; Anti-Bacterial Agents [*therapeutic use]; Chorioamnionitis [*prevention & control]; Endometritis [prevention & control]; Intensive Care Units, Neonatal [utilization]; Randomized Controlled Trials as Topic; Sepsis [prevention & control]; Sulbactam [therapeutic use]

MeSH check words

Female; Humans; Infant, Newborn; Pregnancy



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Hepatitis B vaccination during pregnancy for preventing infant infection (Review)

Sangkomkamhang US, Lumbiganon P, Laopaiboon M

Sangkomkamhang US, Lumbiganon P, Laopaiboon M.
Hepatitis B vaccination during pregnancy for preventing infant infection.
Cochrane Database of Systematic Reviews 2014, Issue 11. Art. No.: CD007879.
DOI: 10.1002/14651858.CD007879.pub3.

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	2
OBJECTIVES	3
METHODS	3
RESULTS	4
DISCUSSION	5
AUTHORS' CONCLUSIONS	5
ACKNOWLEDGEMENTS	5
REFERENCES	5
CHARACTERISTICS OF STUDIES	7
DATA AND ANALYSES	10
APPENDICES	10
WHAT'S NEW	13
HISTORY	14
CONTRIBUTIONS OF AUTHORS	14
DECLARATIONS OF INTEREST	14
SOURCES OF SUPPORT	14
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	15
INDEX TERMS	15

Hepatitis B vaccination during pregnancy for preventing infant infection

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ABSTRACT

Background

Infant hepatitis B infection increases the risk of chronic infection, cirrhosis or liver cancer (hepatocellular carcinoma) in the adult. Perinatal transmission is a common route of infection.

Objectives

To assess the effectiveness and adverse effects of hepatitis B vaccine administered to pregnant women for preventing hepatitis B virus infection in infants.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 August 2014).

Selection criteria

Randomized controlled trials (RCTs) assessing hepatitis B vaccination compared with placebo or no treatment during pregnancy for preventing infant infection. Quasi-RCTs and cross-over studies were not eligible for inclusion.

Data collection and analysis

Two review authors independently assessed trials for inclusion. If any studies had been included, we planned to assess the risk of bias, extract data and check the data for accuracy of all included studies.

Main results

We did not identify any studies for inclusion.

Authors' conclusions

We found no RCTs that assessed the effects of hepatitis B vaccine during pregnancy for preventing infant infection. Consequently, this review cannot provide guidance for clinical practice in this area. However, it does identify the need for well-designed randomized clinical trials to assess the effect of hepatitis B vaccine during pregnancy on the incidence of infant infection and to determine any adverse effects.

PLAIN LANGUAGE SUMMARY

Hepatitis B vaccination during pregnancy for preventing infant infection

Hepatitis B is an infection caused by the hepatitis B virus and occurs worldwide. For infants and children, the two main sources of the infection are transmission from an infected mother or living in an infected household. Perinatal transmission is common in highly endemic areas. Hepatitis B vaccines are available and require a series of three doses over six months. The most common side effects are pain at the vaccination site and mild to moderate fever. Maternal hepatitis B vaccine immunization may be a way of preventing hepatitis B infection in infants before hepatitis B vaccine can be administered and provide protection to the infant. Infected hepatitis B virus infants are more likely to develop complications such as chronic infection, cirrhosis or liver cancer (hepatocellular carcinoma). This review found no evidence from randomized controlled trials regarding the effects of hepatitis B vaccine for preventing infant infection.

BACKGROUND

Description of the condition

Hepatitis B virus (HBV) is an enveloped, double-stranded DNA virus. Hepatitis B is an infection caused by the HBV and it occurs worldwide. The highest rates of HBV carriers are found in developing countries with limited medical facilities. In highly endemic areas of Asia, Africa and the Pacific, approximately 75% of hepatitis B carriers usually acquire the virus perinatally or in childhood (Safary 2000). In western and northern European countries and in North America, HBV infection is relatively rare and acquired primarily in adulthood. HBV infections result in 500,000 to 1.2 million deaths per year caused by chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) (Lavanchy 2004). Globally, HBV causes 60% to 80% of the world's primary liver cancers (Parkin 2001).

Diagnosis of hepatitis is made by biochemical assessment of liver function and coagulation studies (Hollinger 2001). Diagnosis is confirmed by demonstration of specific antigens and/or antibodies. Three clinically useful antigen antibody systems have been identified for hepatitis B: (1) hepatitis B surface antigen (HBsAg) and antibody to HBsAg (anti-HBs IgG); (2) antibody (anti-HBc IgM) and anti-HBc IgG to hepatitis B core antigen (HBcAg); and (3) hepatitis B e antigen (HBeAg) and antibody to HBeAg (anti-HBe) to determine infectivity.

For infants and children, the two primary sources of HBV infection are perinatal transmission from infected mothers and horizontal transmission from infected household contacts. Perinatal transmission is common in hyperendemic areas, especially when HBsAg carrier mothers are also HBeAg positive (Hollinger 2001; Mahoney 1999). For a newborn infant whose mother is positive for both HBsAg and HBeAg, the risk for chronic HBV infection is 70% to 90% by six months postpartum in the absence of post-exposure immunoprophylaxis (Wong 1984). By comparison, the infant risk for chronic infection is less than 10% in the mother who is HBeAg negative (Stevens 1985). Of those persons who are infected with HBV as infants or young children, 25% to 90% become chronic carriers, and approximately 25% of those with chronic infection die prematurely from cirrhosis or liver cancer (hepatocellular carcinoma) (Gitlin 1997; McMahon 1990). Development of chronic HBV infection at an early age increases the risk of HCC more than infection at older age (Hsieh 1992). Nearly 100% of children with HCC were hepatitis B surface antigen seropositive (Chang 1998). Breastfeeding by an HBsAg positive mother does not increase the risk for acquisition of HBV infection in the infant (Beasley 1975).

Description of the intervention

Hepatitis B vaccines are composed of the surface antigen of HBV (HBsAg), and are produced by two different methods: plasma-derived or recombinant DNA (Assad 1999). Plasma-derived vac-

cines, derived from the plasma of HBsAg-positive donors, consist of highly purified, formalin-inactivated and/or heat-inactivated, alum-adsorbed, hepatitis B subviral particles (22 nm) of HBsAg that are free of detectable nucleic acid, and, therefore, non-infectious. Recombinant DNA yeast-derived or mammalian cell-derived vaccines, the S gene (pre-S1, pre-S2, S), is cloned and isolated, inserted into an expression plasmid and introduced into yeast or mammalian cells. The desired protein is expressed and assembled into 22 nm antigenic particles. As on natural HBsAg particles, the epitope that elicits the most important immune response is exposed on the surface of artificial particles. Vaccines used for primary prevention have effectively reduced the risk of infection in most populations (Mahoney 1993). Completion of hepatitis B vaccine programs induces protection in about 95% of recipients (Jackson 2007). Vaccination during pregnancy is safe and provides passive transfer of antibodies to the newborn (Anonymous 1991; Gupta 2003; Levy 1991). There are no known side effects from vaccination, in either pregnant women or their offspring (Grosheide 1993). The most common side effects from hepatitis B vaccination are pain at the injection site and mild to moderate fever (Andre 1989; Greenberg 1993).

Hepatitis B vaccine is given into the deltoid muscle by injection in a series of three doses (De Lalla 1988; Krugman 1981). The first shot is given at the elected date; the second dose a month later; and the third dose six months after the first dose. Vaccine batches should be stored at 2° to 8°C. Freezing destroys the potency of the vaccine. Factors that may reduce the immunogenicity of hepatitis vaccines include age (greater than 40 years), weight, genetics, hemodialysis, HIV infection, immunosuppression, tobacco smoking, subcutaneous injection, injection into the buttocks, and accelerated schedule (Ingardia 1999).

How the intervention might work

The mechanism of hepatitis B vaccination during pregnancy for preventing neonatal infection is the production of maternal antibodies that can be transferred across the placenta and provide the neonate with high antibody titers. This could protect the neonate from horizontal infection until active immunization after birth is protective (Reddy 1994).

Why it is important to do this review

Complex HBV epidemiology makes it difficult to evaluate and compare the effectiveness of different immunization policies. HBV infection rates vary in different parts of the world according to the pattern of hepatitis B transmission. In high endemic populations, transmission during delivery is considered for the main mode of perinatal transmission such as close contact with a caregiver who had HBV infection (Ghendon 1987). Many countries have implemented universal hepatitis B immunization at birth, which pro-

vides long-term protection against infection in more than 90% of healthy people (Shepard 2006). Despite this, some infants who are born to HBV sero-positive mothers have become infected by HBV despite having received passive-active immunoprophylaxis (Ngu 1998). A prevention program by maternal hepatitis B vaccine immunization may be a way of preventing hepatitis B infection in infants before hepatitis B vaccine can be administered and provide protection. However, the ideal plan for hepatitis B vaccine administration during pregnancy, taking into consideration risk factors (high risk of HBV infection or the general population); endemic populations (high or low); and cost effectiveness, is not known.

OBJECTIVES

To assess the effectiveness and adverse effects of hepatitis B vaccine administered to pregnant women for preventing HBV infection in infants.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomized controlled trials (RCTs) of hepatitis B vaccination during pregnancy for preventing infant infection. The randomized units could be individual or clustered (e.g. hospitals). Cross-over trials and quasi-randomized trials were not eligible for inclusion.

Types of participants

All pregnant women who had negative test results of hepatitis B virus serology.

Types of interventions

Hepatitis B vaccine compared with placebo or no treatment.

Types of outcome measures

Primary outcomes

- Incidence of hepatitis B virus infection in infants.

Secondary outcomes

- Hepatitis B antibody for hepatitis B virus (HBs Ab) in newborns up to six months after birth.
- Maternal antibody for hepatitis B virus (HBs Ab).
- Adverse maternal effects such as local reactions at injection site (soreness, swelling, erythema); fatigue; fever; headache.

Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (31 August 2014).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of Embase;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We did not apply any language restrictions.

Data collection and analysis

For methods used in the previous version of this review, *see* [Sangkomkamhang 2011](#).

For the 2014 update, two review authors independently assessed for inclusion the one report identified as a result of the search strategy and excluded it ([Wang 2008](#)) (*see* [Characteristics of excluded studies](#)). If future searches identify trials for inclusion, we will use the methods described in [Appendix 1](#).

RESULTS

Description of studies

Results of the search

The search of the Cochrane Pregnancy and Childbirth Group's Trials Register retrieved 13 studies. Eleven studies did not involve hepatitis B vaccine and were excluded. We sought full reports of the remaining two studies for detailed assessment. We identified only one full report of randomized controlled comparison between two doses and three doses of hepatitis B vaccine in pregnancy. The other study was only in abstract form.

Included studies

There are no included trials in this review.

Excluded studies

We excluded 13 studies, mostly because they assessed hepatitis B immunoglobulin (HBIG) for preventing infant hepatitis B infection, or they were not RCTs. One RCT compared two doses versus three doses of hepatitis B vaccine. For details, *see* [Characteristics of excluded studies](#).

Risk of bias in included studies

Not applicable as there are no included studies.

Allocation

Not applicable as there are no included studies.

Blinding

Not applicable as there are no included studies.

Incomplete outcome data

Not applicable as there are no included studies.

Selective reporting

Not applicable as there are no included studies.

Other potential sources of bias

Not applicable as there are no included studies.

Effects of interventions

Not applicable as there are no included studies.

DISCUSSION

Summary of main results

We found no studies to evaluate the effectiveness of hepatitis B virus during pregnancy in preventing neonatal infection.

Overall completeness and applicability of evidence

There are no studies that met our inclusion criteria.

Quality of the evidence

There are no studies that met our inclusion criteria.

Potential biases in the review process

We followed the process of review as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). There were no conflicts of interest with the review authors.

Agreements and disagreements with other studies or reviews

There are no other reviews and studies related to the efficacy and side effects of hepatitis B vaccine during pregnancy for preventing infant infection.

AUTHORS' CONCLUSIONS

Implications for practice

This review found that there were no randomized controlled trials (RCTs) assessing the effects of hepatitis B vaccine during pregnancy for preventing infant infection. Consequently, this review cannot provide guidance for clinical practice in this area.

Implications for research

This systematic review has identified the need for well-designed RCTs to assess the benefits and adverse effects of hepatitis B vaccine during pregnancy compared with placebo or no treatment for preventing infant infection. The trials should include clinical outcomes of the incidence of hepatitis B virus infection in infants.

There were many studies of using hepatitis B immunoglobulin (HBIG) during pregnancy to prevent neonatal infection. Further meta-analyses are needed to determine the effectiveness and adverse effects of HBIG administered to pregnant women for preventing HBV infection in infants.

ACKNOWLEDGEMENTS

As part of the pre-publication editorial process, Sangkomkarnhang 2011 was been commented on by three peers (an editor and two referees who are external to the editorial team) and the Group's Statistical Adviser.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Gupta 2003	Study on immunogenicity and safety of HBV vaccine, comparisons of 2 doses HBV vaccine versus 3 doses in HBsAg negative pregnant women
Li 2003	Study on 3 comparisons of HBIG versus lamivudine versus no treatment in HBsAg positive pregnant women for prevention of intrauterine infection of HBV
Li 2004	Study on HBIG versus placebo in HBsAg positive pregnant women for prevention of intrauterine infection of HBV
Patwardhan 2005	Study on HBV vaccine in both non-pregnant and pregnant women for prevention of vertical transmission. Abstract only
Wang 2008	Study on HBIG in HBsAg and HBeAg positive pregnant women for prevention of mother to infant HBV transmission
Xu 2004	Study on lamivudine versus placebo in late pregnancy for mothers with high viremia, in addition to HBV vaccination plus HBIG for the infants for prevention of mother-to-child transmission of HBV
Xu 2006	Study on HBIG versus placebo in HBeAg and HBsAg positive pregnant women for prevention of intrauterine infection of HBV
Xu 2009	Study on lamivudine in highly viremic and late pregnancy for prevention of perinatal transmission of HBV infection
Yu 2003	Study on HBIG in HBsAg positive pregnant women for prevention of intrauterine infection. This was an observational study
Yuan 2006	Study on 3 doses of HBIG in seropositive for hepatitis B e antigen (HBeAg) pregnant women versus no treatment for prevention of mother-to-child transmission of HBV
Yue 1999	Study on HBIG in seropositive for hepatitis B surface (HBsAg) antigen pregnant women versus no treatment for prevention of mother-to-child transmission of HBV
Zhu 1997	Study on HBIG in HBV carriers pregnant women versus no treatment for prevention of mother-to-child transmission of HBV
Zhu 2003	Study on 3 doses of HBIG in HBsAg carrier pregnant women versus no treatment for prevention of intrauterine transmission of HBV

HBeAG: hepatitis B e antigen

HBIG: hepatitis B immunoglobulin

HBsAg: hepatitis B surface antigen

HBV: hepatitis B virus

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix I. Methods for data collection and analysis in subsequent updates of this review

Selection of studies

Two review authors will independently assess for inclusion all the potential studies identified as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult the third review author.

Data extraction and management

We will design a form to extract data. For eligible studies, two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult the third review author. We will enter data into Review Manager software ([RevMan 2014](#)) and check for accuracy.

When information regarding any of the above is unclear, we plan to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We will resolve any disagreements by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We will assess the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We will assess the methods as:

- low risk of bias (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.

We will assess methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomization);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We will assess the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We will describe for each included study any important concerns we have about other possible sources of bias.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - see Sensitivity analysis.

The quality of the evidence will be assessed using the GRADE approach (Schunemann 2009) in order to assess the quality of the body of evidence relating to the following outcomes for the main comparisons:

1. Incidence of hepatitis B virus infection in infants.

GRADEprofiler (GRADE 2008) will be used to import data from Review Manager 5.3 (RevMan 2014) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes will be produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded

from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardized mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomized trials

We will include cluster-randomized trials in the analyses along with individually-randomized trials. We will adjust their sample size using the methods described in the *Handbook* [Section 16.3.4 or 16.3.6] using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomized trials and individually-randomized trials, we plan to synthesize the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomization unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomization unit and perform a subgroup analysis to investigate the effects of the randomization unit.

Cross-over trials

Other unit of analysis issues

It is unlikely that cross-over designs will be a valid study design for Pregnancy and Childbirth reviews, and so if identified, we will exclude them.

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomized to each group in the analyses, and all participants will be analyzed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomized minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the Tau^2 , I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if the I^2 is greater than 30% and either the Tau^2 is greater than zero, or there is a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We will carry out statistical analysis using the Review Manager software (RevMan 2014). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average of the range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

If we use random-effects analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of τ^2 and I^2 .

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

We plan to carry out the following subgroup analyses:

1. low risk of hepatitis B virus (HBV) infection versus high risk (as defined by authors e.g. injection drug users, healthcare workers) of HBV infection;
2. low endemic setting versus high endemic setting of HBV infection;
3. vaccination schedule (e.g. three doses versus two doses regimen);
4. maternal negative versus positive for marker of hepatitis B virus serology.

The following outcomes will be used in subgroup analysis:

1. Incidence of hepatitis B virus infection in infants.

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2014). We will report the results of subgroup analyses quoting the χ^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We plan to carry out sensitivity analyses to explore the effect of trial quality assessed by concealment of allocation, high attrition rates, or both, with poor quality studies being excluded from the analyses in order to assess whether this makes any difference to the overall result.

WHAT'S NEW

Last assessed as up-to-date: 31 August 2014.

Date	Event	Description
31 August 2014	New citation required but conclusions have not changed	Review updated. No included studies.

(Continued)

31 August 2014	New search has been performed	Search updated. One new report identified and excluded (Wang 2008).

HISTORY

Protocol first published: Issue 3, 2009

Review first published: Issue 3, 2011

Date	Event	Description
12 April 2011	Amended	Plain language summary heading edited.

CONTRIBUTIONS OF AUTHORS

Ussanee S Sangkomkarnhang drafted the review, Pisake Lumbiganon and Malinee Laopaiboon revised and approved the final version of the review ([Sangkomkarnhang 2011](#)) and the 2014 update.

DECLARATIONS OF INTEREST

Malinee Laopaiboon received an honorarium from the Thailand Research Fund, a non-profit organization. This fund partially subsidizes Thai Cochrane reviewers to do and update Cochrane reviews.

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Internal sources

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External sources

- Thai Cochrane Network, Thailand.
- Thailand Research Fund (Senior Research Scholar), Thailand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The methods have been updated in accordance with the latest *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

Types of participants has been changed from 'All pregnant women unaware of marker results of hepatitis B virus serology' to 'All pregnant women who had negative test results of hepatitis B virus serology'.

INDEX TERMS

Medical Subject Headings (MeSH)

*Vaccination; Hepatitis B [*transmission]; Hepatitis B Vaccines [*administration & dosage]; Infectious Disease Transmission, Vertical [*prevention & control]; Pregnancy Complications, Infectious [*prevention & control]

MeSH check words

Adult; Female; Humans; Infant; Pregnancy



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Adjuvant chemotherapy after concurrent chemoradiation for locally advanced cervical cancer (Review)

Tangjitgamol S, Katanyoo K, Laopaiboon M, Lumbiganon P, Manusirivithaya S, Supawattanabodee B

Tangjitgamol S, Katanyoo K, Laopaiboon M, Lumbiganon P, Manusirivithaya S, Supawattanabodee B.

Adjuvant chemotherapy after concurrent chemoradiation for locally advanced cervical cancer.

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	3
METHODS	4
RESULTS	6
Figure 1.	7
Figure 2.	10
Figure 3.	10
Figure 4.	11
Figure 5.	11
Figure 6.	11
Figure 7.	12
Figure 8.	12
DISCUSSION	12
Figure 9.	14
Figure 10.	15
AUTHORS' CONCLUSIONS	15
ACKNOWLEDGEMENTS	16
REFERENCES	16
CHARACTERISTICS OF STUDIES	18
DATA AND ANALYSES	26
Analysis 1.1. Comparison 1 Survival, Outcome 1 Progression-free survival.	26
Analysis 1.2. Comparison 1 Survival, Outcome 2 Overall survival.	27
Analysis 2.1. Comparison 2 Failure after treatment, Outcome 1 Total failure after treatment.	27
Analysis 2.2. Comparison 2 Failure after treatment, Outcome 2 Local failure.	28
Analysis 2.3. Comparison 2 Failure after treatment, Outcome 3 Distant failure.	28
Analysis 3.1. Comparison 3 Adverse events, Outcome 1 Anaemia.	29
Analysis 3.2. Comparison 3 Adverse events, Outcome 2 Thrombocytopenia.	29
ADDITIONAL TABLES	29
APPENDICES	33
CONTRIBUTIONS OF AUTHORS	35
DECLARATIONS OF INTEREST	36
SOURCES OF SUPPORT	36
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	36
INDEX TERMS	36

Adjuvant chemotherapy after concurrent chemoradiation for locally advanced cervical cancer

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ABSTRACT

Background

Current standard treatment for patients with cervical cancer who have locally advanced stage disease (International Federation of Gynecology and Obstetrics (FIGO) stage IIB to IVA) is concurrent chemoradiation therapy (CCRT). However, less than two-thirds of patients in this group survive for longer than five years post treatment. Adjuvant chemotherapy (ACT) can be given in an attempt to improve survival by eradicating residual disease in the pelvis and treating occult disease outside the pelvic radiation field. However, inconsistency in trial design, inclusion criteria for participants, interventions and survival benefit has been noted among trials of ACT after CCRT for locally advanced cervical cancer (LACC).

Objectives

To evaluate the effect of adjuvant chemotherapy (ACT) after concurrent chemoradiation (CCRT) on survival of women with locally advanced cervical cancer compared with CCRT alone.

Search methods

We searched the Cochrane Gynaecological Review Group Trial Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and conference proceedings to March 2014. We handsearched citation lists of relevant studies.

Selection criteria

Randomised controlled trials (RCTs) comparing CCRT alone versus CCRT plus ACT were included. Patients were diagnosed with cervical cancer FIGO stage IIB to IVA with a histopathology of squamous cell carcinoma, adenosquamous cell carcinoma, adenocarcinoma or undifferentiated carcinoma.

Data collection and analysis

Two review authors (ST, KK) selected relevant trials, extracted data, assessed risk of bias independently, compared results and resolved disagreements by discussion.

Main results

We identified two RCTs involving 978 women with cervical cancer stage IIB to IVA. As the trials were significantly different clinically, we did not perform meta-analyses. One industry-funded trial involving 515 women compared CCRT (cisplatin) versus CCRT (cisplatin and gemcitabine) plus ACT (two additional cycles). This trial reported significant improvement in progression-free survival (PFS) and overall survival (OS) in women who were given CCRT plus ACT compared with those treated with CCRT alone: Three-year PFS was 74.4% versus 65.0% (hazard ratio (HR) 0.68, 95% confidence interval (CI) 0.49 to 0.95, P value 0.027), and three-year OS was 80% versus 69% (HR 0.68, 95% CI 0.49 to 0.95, P value 0.022). However, as the CCRT chemotherapy differed between the two arms, we considered the findings to be at high risk of bias.

The second trial was a four-arm study from which we extracted data on 463 women in two study arms receiving CCRT (intravenous mitomycin C and oral 5-fluorouracil (5-FU)) or CCRT plus ACT (oral 5-FU for three cycles). The HR for OS in women who received ACT after CCRT compared with the HR for OS in those who were given CCRT alone was 1.309 (95% CI 0.795 to 2.157), and the HR for disease-free survival (DFS) was 1.125 (95% CI 0.799 to 1.586).

Haematological adverse events were more common in the ACT arms of both trials. Quality of life (QoL) was not reported in either trial.

Authors' conclusions

With limited data from only two trials, we found insufficient evidence to support the use of ACT after CCRT. Future large trials are required to demonstrate efficacy, toxicities and QoL.

PLAIN LANGUAGE SUMMARY

Can additional chemotherapy after initial treatment for locally advanced stage cervical cancer reduce recurrence and extend life?

The issue

Standard treatment for locally advanced stage cervical cancer (stage IIB to IVA) is 'concurrent chemoradiation' when anticancer drugs are given during the same treatment period as pelvic radiotherapy (radiation therapy to lower abdomen). However, the tumour may remain (residual cancer) or may come back (recurrent cancer) after this standard treatment. This review evaluated whether giving additional anticancer drugs (ACTs) after standard treatment could help women with locally advanced cervical cancer to live longer compared with standard treatment alone.

How we conducted the review

We searched the literature to March 2014 and identified two randomised controlled trials comparing standard treatment versus standard treatment plus ACT in women with locally advanced cervical cancer. Two review authors assessed these studies and collected data independently.

Findings

The two studies were very different; therefore we could not pool their data. One trial conducted internationally between 2002 and 2004, involving 515 women, found that cancer took longer to return in women receiving ACT (cisplatin and gemcitabine), and more women in the ACT group were alive after three years than in the standard treatment group (80% versus 69%). We considered the findings to be at high risk of bias in this trial, as women were given different drugs during standard treatment, and so the overall effect of the study treatment could not be attributed to the ACT alone. The other trial, which was conducted in several hospitals in Thailand between 1988 and 1994, involved 463 women. ACT (5-fluorouracil) did not improve the length of survival or the time taken for cancer to return in women in this trial. A trend towards increased side effects was reported in the ACT arms of both studies.

Conclusions

We found insufficient evidence to support giving additional anticancer drugs to women who have received standard treatment for locally advanced cervical cancer, as currently only limited data are available from two very different trials.

BACKGROUND

Description of the condition

Worldwide, cervical cancer is the fourth most common cancer in women, with an estimated 528,000 new cases and 266,000 deaths in 2012 (Ferlay 2013). Most cervical cancer cases (84%, or 445,000 cases) and deaths (87%, or 230,000 cases) occurred in less developed regions (Ferlay 2013). In addition to a higher incidence of cervical cancer in less developed regions, patients in these areas have a higher proportion of locally advanced stages, including stage IIB to IVA of the International Federation of Gynecology and Obstetrics (FIGO) staging classification, or advanced stage IVB cancers (Moore 2010). This is due in part to lack of co-ordinated screening programmes and/or lack of access to radiotherapy, leading to poorer overall survival. Thus, seeking further means of improving treatment outcomes for advanced or locally advanced cervical cancer (LACC) is required.

Description of the intervention

Concurrent chemoradiation therapy (CCRT) is a type of treatment in which chemotherapy is given at the same time as radiation therapy. Chemotherapy serves as a radiosensitiser that enhances the activity of radiation, and as a direct cytotoxin to local tumour cells and subclinical distant metastases beyond the radiation area (Rose 2002). It is currently a standard treatment for patients with LACC. This combined treatment appeared to improve survival outcomes compared with radiation therapy alone (Green 2005), with overall survival rates ranging from 60% to 65% (Cochrane Meta-Analysis Collaboration 2008). However, local and distant failures (17% and 18%, respectively) of LACC after CCRT were still encountered (Eifel 2004). Interventions provided to improve treatment outcomes include chemotherapy administered before CCRT (neoadjuvant chemotherapy) (McCormack 2013 (a); McCormack 2013 (b); Singh 2013) and additional chemotherapy given after the standard treatment, which is referred to as 'consolidation chemotherapy' or 'adjuvant chemotherapy' (ACT) (Choi 2007; Dueñas-González 2011; Lorvidhaya 2003; Tang 2012; Vrdoljak 2005; Vrdoljak 2006; Zhang 2010).

How the intervention might work

The objective of adjuvant chemotherapy after completion of radiation therapy, or CCRT, is to eradicate tumour cells outside of the radiation field. The role of ACT has been explored in several studies or trials involving LACC (Choi 2007; Choi 2010; Domingo 2009; Dueñas-González 2011; Lorvidhaya 2003; Tang 2012; Vrdoljak 2006; Wong 1999; Zhang 2010). All single-arm phase II studies (Choi 2007; Domingo 2009; Vrdoljak 2006; Zhang 2010) that evaluated the role of ACT in LACC reported a higher response rate than those that evaluated the role of CCRT alone. Overall survival rates greater than 80% to 90% achieved with CCRT followed by ACT were higher than the 60% to 65% rates obtained with CCRT alone (Cochrane Meta-Analysis Collaboration 2008).

Why it is important to do this review

Concurrent chemoradiation therapy (CCRT) is the current standard treatment for locally advanced cervical cancer (LACC); however, it can yield only a 60% to 65% survival rate (Cochrane Meta-Analysis Collaboration 2008). Adjuvant chemotherapy after CCRT is therefore one possible way to extend the survival of patients with LACC because it may further reduce or eradicate any residual disease, including occult disease outside the pelvic radiation field. Although the survival benefit derived from ACT after CCRT has been demonstrated in some studies, evidence is limited. Furthermore, each study has specific characteristics vis-à-vis the population included and the different types of chemotherapy regimen given, especially between two study arms in the same trial. Without clear benefit of ACT after CCRT, no definitive recommendation or clinical practice guideline can be provided for its use. As chemotherapy can cause toxicities, potential survival advantages must outweigh these disadvantages, hence a systematic review to evaluate the efficacy and toxicity of this treatment option is warranted.

OBJECTIVES

To evaluate the effect of adjuvant chemotherapy (ACT) after concurrent chemoradiation (CCRT) on survival of women with locally advanced cervical cancer compared with CCRT alone.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Women ≥ 18 years of age with a diagnosis of cervical cancer, FIGO stage IIB to IVA, and a histopathology of squamous cell carcinoma, adenosquamous cell carcinoma, adenocarcinoma or undifferentiated carcinoma. All patients had concurrent chemoradiation (CCRT) before receiving adjuvant chemotherapy (ACT).

Types of interventions

- Intervention: adjuvant or additional chemotherapy (ACT) given after standard treatment of chemotherapy and radiation during the same period (CCRT).
- Comparator: standard treatment with CCRT, then no further treatment.

Types of outcome measures

Primary outcomes

- Overall survival, analysed from date of randomisation until death or the participant's last visit.
- Progression-free survival analysed from date of randomisation until appearance of a new lesion during treatment, or a greater than 20% or 25% increase in local tumour size by RECIST (Response Evaluation Criteria In Solid Tumors) (Eisenhauer 2009) or WHO (World Health Organization) (Miller 1981) criteria, respectively.

Secondary outcomes

- Response rates after completion of CCRT, and after ACT.
- Recurrence rate after treatment with CCRT, and after ACT.
- Quality of life, measured using a scale that has been validated through reporting of norms in a peer-reviewed publication.
- Severe toxicities and adverse events in study arm versus control arm, classified according to CTCAE 2006.

Grades of toxicity were grouped as:

- haematological (leucopenia, anaemia, thrombocytopenia, neutropenia, haemorrhage);

- gastrointestinal (nausea, vomiting, anorexia, diarrhoea, liver, proctitis);
- genitourinary;
- skin (stomatitis, mucositis, alopecia, allergy);
- neurological (peripheral and central); or
- pulmonary.

Search methods for identification of studies

We searched for papers without restriction of languages and arranged translation as necessary.

Electronic searches

We searched the following electronic databases.

- Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 1) (Appendix 1).
- MEDLINE to March 2014 (Appendix 2).
- EMBASE to March 2014 (Appendix 3).

We identified all relevant articles on PubMed using the 'related articles' feature and performed further searches for other published articles.

Searching other resources

Unpublished and grey literature

We searched the following for ongoing trials.

- metaRegister of Controlled Trials (mRCT) (<http://www.controlled-trials.com/mrct/>).
- Physicians Data Query (<http://www.cancer.gov/cancertopics/pdq/cancerdatabase>).
- ClinicalTrials.gov (<http://clinicaltrials.gov/>).
- National Cancer Institute (<http://www.cancer.gov/clinicaltrials>).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (<http://apps.who.int/trialsearch/>).

We identified ongoing trials with published information on study design and inclusion and exclusion criteria (Mileshkin 2010; Tangjitgamol 2014). We found that recruitment for both trials is ongoing.

We searched electronic databases such as Zetoc (<http://zetoc.mimas.ac.uk/>) and Ohio College Library Center (OCLC) WorldCat Dissertations and Theses (WorldCatDissertations) (<http://www.oclc.org/support/documentation/firstsearch/databases/dbdetails/details/worldcatdissertations.htm>) for conference proceedings and abstracts.

Handsearching

We handsearched the citation lists of included studies and key textbooks and contacted experts in the field to identify further reports of trials. We also handsearched the following sources for previous systematic reviews and reports of conferences.

- Gynecologic Oncology (Annual Meeting of the American Society of Gynecologic Oncologists).
- *International Journal of Gynecological Cancer* (Biannual Meeting of the International Gynecologic Cancer Society and Biannual Meeting of the European Society of Gynaecologic Oncology).
- *British Journal of Cancer*.
- British Cancer Research Meeting.
- Annual Meeting of European Society of Medical Oncology.
- Annual Meeting of the American Society of Clinical Oncology.

Data collection and analysis

Selection of studies

Two review authors (ST, KK) independently examined search results and obtained and excluded records that clearly did not meet our inclusion criteria. We obtained copies of the full text of potentially relevant references. The two review authors (ST, KK) independently assessed eligibility of the retrieved full-text articles. Disagreements were resolved by discussion between the two review authors and by consultation with a third review author (PL). Reasons for exclusion were documented.

Data extraction and management

Two review authors (ST, KK) extracted data independently using a data abstraction form specially designed for the review. The two review authors resolved differences by discussion or by appeal to a third review author (PL) when necessary. For included studies, the following data were extracted.

- Author, year of publication and journal citation (including language).
- Country.
- Setting.
- Inclusion and exclusion criteria.
- Study design, methodology.
- Study population (total number enrolled; participant characteristics; participant age; co-morbidities; other baseline characteristics).
- Intervention details (CCRT-regimen, dosage, cycles of treatment; radiation therapy-radiation therapy technique (external pelvic radiation therapy, extended field radiation therapy, brachytherapy), radiation machine or instrument (cobalt, linear accelerator), type of brachytherapy (low-dose or

high-dose rate), doses; ACT-regimen, dosage, cycles of treatment).

- Comparison (primary and secondary outcomes between the two arms).
- Risk of bias in the study ([Assessment of risk of bias in included studies](#)).
- Duration of follow-up.
- Outcomes (outcome definition and unit of measurement (if relevant); for adjusted estimates, we recorded variables adjusted for during analyses).
- Results (number of participants allocated to each intervention group, total number analysed for each outcome, missing participants).

Data on all participants in the groups to which they were originally randomly assigned (intention-to-treat) were extracted. We noted the time points at which outcomes were collected and reported. Results were extracted as follows.

- Time-to-event data (survival and disease progression): We estimated the log of hazard ratio using the methods of [Parmar 1998](#).
- Dichotomous outcomes (e.g. adverse events or deaths): We extracted the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed at endpoint, to estimate the risk ratio.
- Continuous outcomes (e.g. quality of life measures): No data were available.

Assessment of risk of bias in included studies

Risk of bias in included trials was assessed using the tool of The Cochrane Collaboration for assessing risk of bias ([Higgins 2011; Appendix 4](#)).

- Selection bias (random sequence generation and allocation concealment).
- Performance bias (not applicable because clinicians were aware of interventions).
- Detection bias (blinding of outcome assessment).
- Attrition bias (high rates of incomplete outcome data and trials with $\geq 20\%$ missing data were assessed as having high risk of bias).
- Reporting bias (selective reporting of outcomes).

Two review authors (ST, KK) applied the risk of bias tool independently; differences were resolved by discussion or by appeal to the third and fifth review authors (PL, ML). We summarised results in both a risk of bias graph and a risk of bias summary. Results of meta-analyses were interpreted in light of the findings with respect to risk of bias.

Measures of treatment effect

We planned to pool the results of included studies in meta-analyses if adequate numbers of clinically similar studies were available. We would use the following measures of the effects of treatment.

- Dichotomous outcomes: Risk ratio (RR) and 95% confidence interval (CI) were calculated for each trial.
- Time-to-event data: Hazard ratio (HR) and 95% CI were calculated for each study.

Dealing with missing data

We did not impute missing outcome data.

Assessment of heterogeneity

We planned to assess heterogeneity between studies by visual inspection of forest plots, by estimation of the percentage of inconsistency between trials that could not be ascribed to sampling variation (Higgins 2003) and by a formal statistical test of the significance of the heterogeneity (Deeks 2001).

Assessment of reporting biases

We intended to examine funnel plots corresponding to meta-analyses of the primary outcome to assess the potential for small-study effects such as publication bias if a sufficient number of studies (i.e. more than 10) were identified.

Data synthesis

We intended that if sufficient clinically similar studies were available, we would conduct meta-analyses using the Cochrane Collaboration's statistical software (Review Manager 2012) using a fixed-effect model. If data were statistically or clinically heterogeneous, we planned to use the random-effects model with inverse variance weighting (DerSimonian 1986).

Subgroup analysis and investigation of heterogeneity

To investigate heterogeneity of the primary outcomes, we planned to perform subgroup analyses with trials grouped by:

- type of chemotherapeutic regimen (platinum versus non-platinum-based);
- stage of disease (stage IIB versus stage III to IVA);
- radiation therapy technique (external pelvic radiation therapy, radiation machine (cobalt or linear accelerator), brachytherapy, extended field radiation therapy); and
- histopathology (squamous cell carcinoma versus others).

Factors such as age, stage, type of intervention, length of follow-up and risk of bias status in interpretation of any heterogeneity would be considered.

Sensitivity analysis

We would perform sensitivity analyses by excluding studies at high risk of bias.

RESULTS

Description of studies

See [Characteristics of included studies](#) and [Characteristics of excluded studies](#).

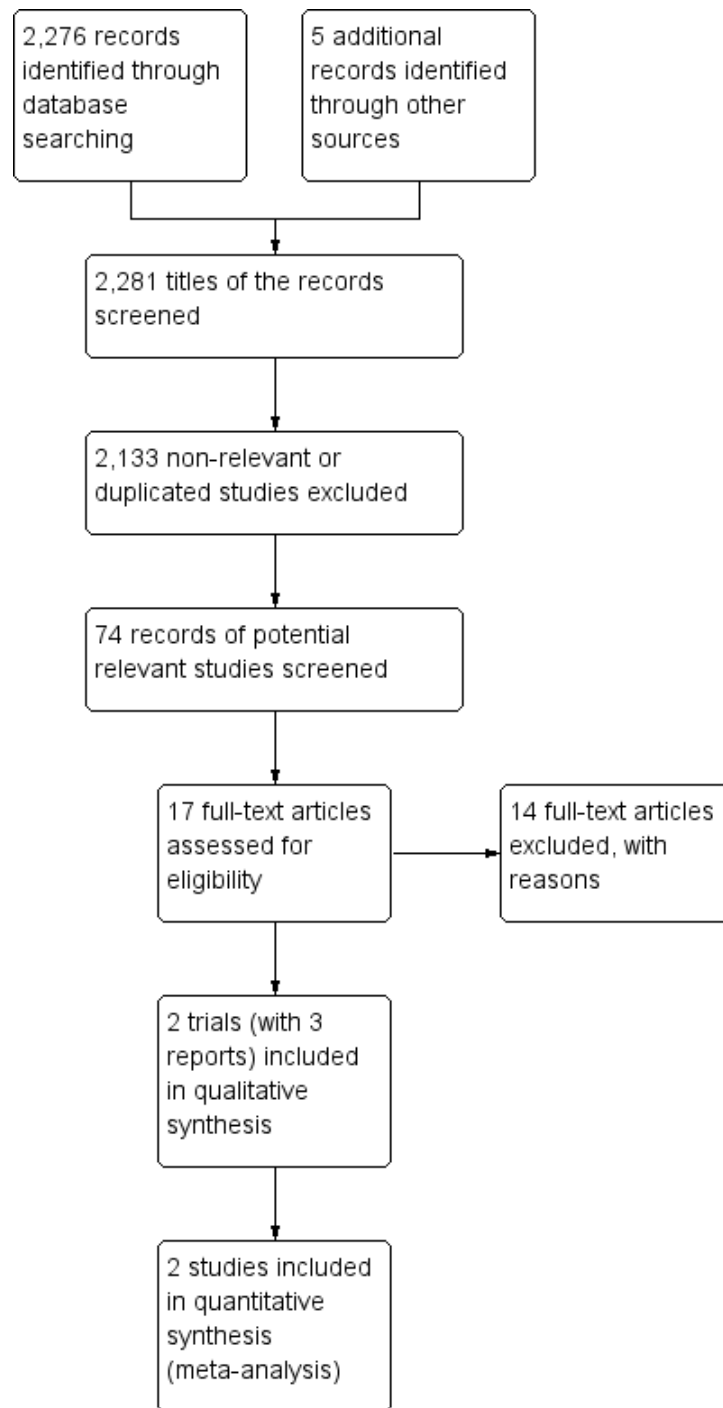
Results of the search

A MEDLINE search identified 598 studies. A similar search of EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL) and the Specialised Register revealed 941 studies, 263 studies and 253 studies, respectively. Reference lists were checked, and handsearching of journals and congress abstracts yielded five additional studies.

A total of 74 articles were selected from the first sift. After 18 duplicates and 39 other abstracts were removed, 17 possibly eligible studies were retrieved for more detailed analysis. We found eight RCTs (Chiara 1994; Dueñas-González 2011; Kantardzic 2004; Lorvidhaya 2003; Tang 2012; Vishnevskaya 1999; Wang 2010; Wong 1999). Two RCTs met the inclusion criteria and were included in this review (Dueñas-González 2011; Lorvidhaya 2003). One study (Dueñas-González 2011) subsequently reported a subgroup analysis to determine prognostic factors for participants (Dueñas-González 2012). Six trials were excluded for one or more of the following reasons: Neoadjuvant chemotherapy was given as well as adjuvant chemotherapy (Chiara 1994; Tang 2012; Vishnevskaya 1999); only radiation was used in either of the control arms (Kantardzic 2004; Vishnevskaya 1999; Wang 2010; Wong 1999) or in both arms (Chiara 1994).

The eight remaining non-randomised studies were excluded for the following reasons: only radiation provided or phase II studies without a comparative arm (Choi 2007; Domingo 2009; Kim 2012; Mahasittiwat 2011; McCaffrey 2011; Vrdoljak 2006); prospective matched case comparison without randomisation (Choi 2010); or a preliminary report of one study (Vrdoljak 2005). See QUOROM (Quality of Reporting of Meta-analyses) statement flow diagram (Figure 1).

Figure 1. Study flow diagram.



Included studies

We found three reports from two RCTs (Dueñas-González 2011; Lorvidhaya 2003). Dueñas-González 2011 described the results of their subgroup analysis in a subsequent report (Dueñas-González 2012), details of which are provided in the [Characteristics of included studies](#).

Design and setting

Two RCTs were included. One (Lorvidhaya 2003) was undertaken in Thailand as a multi-centre trial between January 1988 and November 1994. The other (Dueñas-González 2011) was conducted in Argentina, Bosnia and Herzegovina, India, Mexico, Pakistan, Panama, Peru and Thailand between May 2002 and March 2004.

Participants

Two trials included a total of 978 participants with stage IIB to IVA cervical cancer.

Lorvidhaya 2003 included in the study 926 women with a performance status 2 or less, according to the Eastern Cooperative Oncology Group. The histopathology had to be squamous cell carcinoma, adenocarcinoma or adenosquamous cell carcinoma. For women with stage IIB disease, the central tumour had to be larger than 3 cm and/or had to involve more than half of the parametrium.

Dueñas-González 2011 included 515 women with cervical cancer who had Karnofsky performance score ≥ 70 . Tumours of squamous cell carcinoma, adenocarcinoma, adeno/squamous carcinoma and poorly differentiated carcinoma were included. Women with enlarged para-aortic lymph node > 1 cm, proven by fine-needle aspiration to have metastatic cancer, were excluded.

Intervention

The Lorvidhaya trial (Lorvidhaya 2003), which aimed mainly to study the efficacy of CCRT and the role of ACT, randomly assigned participants with LACC to four treatment arms. The standard arm received only radiation therapy (RT) (arm 1, $n = 242$), while the three study arms received RT with ACT (arm 2, $n = 221$) and CCRT without (arm 3, $n = 233$) or with ACT (arm 4, $n = 230$). Radiation was given with Co-60 or a linear accelerator machine. The external beam pelvic radiation (EBRT) dose was 40 to 50 Gy given to whole pelvis and pelvic lymph node. Intracavitary radiation was given according to the practice in each participating centre as four applications of high dose rate or one to two applications of medium dose rate. Chemotherapy given during radiation therapy consisted of intravenous mitomycin C

plus oral 5-FU. The drug used in an adjuvant setting was oral 5-FU given for three cycles: drug taken for four weeks with a two-week rest between cycles. Only two arms (CCRT plus ACT versus CCRT alone) were relevant to our review question, therefore only data on the 233 participants given CCRT (arm 3) and the 230 participants receiving CCRT plus ACT (arm 4) were extracted for the review.

The Dueñas-González trial (Dueñas-González 2011) randomly assigned participants to two treatment arms. The study arm received CCRT followed by ACT (arm A, $n = 259$), while the control arm was given only CCRT (arm B, $n = 256$). Radiation equipment consisted of cobalt-60 (Co-60) or a linear accelerator. The EBRT dose was 50.4 Gy, and a low or intermediate dose rate of brachytherapy was given immediately after chemoradiation. Chemotherapy used concurrently with RT included six cycles of intravenous weekly cisplatin plus gemcitabine in the study arm and only cisplatin in the control arm. Two weeks after completion of brachytherapy, participants in the study arm received two additional cycles of tri-weekly cisplatin plus gemcitabine.

Compliance and follow-up

In Lorvidhaya 2003, 13 participants with small cell carcinoma (six in the CCRT group and seven in the CCRT plus ACT group; approximately 3% both) were excluded from the analysis. After a median follow-up of 89 months, 12 (5%) and 19 (8%) of the participants in both arms were lost to follow-up and received incomplete treatment. Reasons were not specified. These participants were censored as having failure of treatment. No information was provided on the compliance of participants taking oral chemotherapy.

In Dueñas-González 2011, the median follow-up was 46.9 months. The numbers of participants who discontinued treatment were 42 in arm A (CCRT plus ACT) and 11 in arm B (CCRT alone) (P value < 0.001), most commonly as the result of adverse effects. In the CCRT phase, the median number of gemcitabine and cisplatin cycles received in arm A was five (range one to six cycles), and the median number of cycles of cisplatin administered in arm B was six (range one to six cycles). In the ACT phase of arm A, 86.2% of participants received at least one cycle, and 76.5% received both cycles of ACT. Although median radiation doses were similar in the two treatment arms, the period of RT was longer in arm A: 49 days versus 45 days (P value < 0.001).

Outcomes

Lorvidhaya 2003 reported overall survival and progression-free survival (PFS). Dueñas-González 2011 reported overall survival, disease-free survival (DFS) and adverse events.

Excluded studies

Of 17 possibly eligible studies, 14 were excluded: six were RCTs, and eight were phase II prospective trials.

Six RCTs were excluded for one or more of the following reasons: neoadjuvant chemotherapy was also given aside from ACT (Chiara 1994; Tang 2012; Vishnevskaya 1999); only radiation was used in either the control arm (Kantardzic 2004; Vishnevskaya 1999; Wang 2010; Wong 1999) or both arms (Chiara 1994).

Of the eight remaining non-randomised studies, all were excluded for the following reasons: providing radiation only, phase II studies without a comparative arm (Choi 2007; Domingo 2009; Kim 2012; Mahasitawat 2011; McCaffrey 2011; Vrdoljak 2006), prospective matched case comparison without randomisation (Choi 2010) or a preliminary report of one study (Vrdoljak 2005).

See [Characteristics of excluded studies](#).

Risk of bias in included studies

Allocation

In [Lorvidhaya 2003](#), randomisation was stratified according to each individual centre among the six centres joining in the trial. No information was provided regarding the method and the centre or site responsible for randomisation as well as allocation concealment. We assessed this as unclear risk.

In [Dueñas-González 2011](#), participants were randomly assigned to CCRT plus ACT or CCRT alone at week 0 according to the Pocock and Simon algorithm by disease stage (IIB versus III to IVA), tumour diameter (< versus $\geq$ 5 cm), investigational centre, radiation equipment (cobalt-60 versus linear accelerator) and age (< versus $\geq$ 55 years). The random allocation sequence was generated by central telephone of the pharmaceutical company providing the research funding (Eli Lilly, Indianapolis, IN, USA). Allocation was concealed until interventions were assigned. This has been deemed to show low risk of bias.

Blinding

No blinding during treatment was reported in either trial ([Dueñas-González 2011](#); [Lorvidhaya 2003](#)). This is believed to show high risk of bias.

Incomplete outcome data

After randomisation, [Lorvidhaya 2003](#) identified six participants in the CCRT group and seven in the CCRT plus ACT group (approximately 3% both) who had small cell carcinoma and were excluded from the analysis. After a median follow-up of 89 months, 31 participants in both arms (12% or 5% in the CCRT group and 19% or 8% in the CCRT plus ACT group) were lost to follow-up

and received incomplete treatment. Reasons were not specified. Participants were censored as having failure of treatment.

Among the 515 participants who were randomly assigned in [Dueñas-González 2011](#), one who was allocated to CCRT was given both CCRT and adjuvant chemotherapy. A total of 53 participants (approximately 10%) discontinued treatment. After a median follow-up period of 46.9 months, a total of 56 participants (approximately 11%) were lost to follow-up by the end of the study. Numbers and reasons for loss to follow-up were similar in the two treatment arms.

We determined both trials as having low risk of bias.

Selective reporting

All outcomes in [Lorvidhaya 2003](#) were reported according to the protocol. Nevertheless, no information was provided on the timing of adverse events.

Although the primary endpoint in [Dueñas-González 2011](#) was changed from OS to PFS after completion of enrolment, all outcomes specified in the protocol were reported. Survival analyses were performed by an intention-to-treat approach (including the one participant who had a treatment cross-over), and toxicities were analysed for safety according to the actual treatment received. We determined that both trials had low risk of bias.

Other potential sources of bias

No imbalance in baseline characteristics between the two arms was reported in either of the two studies ([Dueñas-González 2011](#); [Lorvidhaya 2003](#)). However, an important difference in CCRT treatment between groups was found in one study ([Dueñas-González 2011](#)). The control arm received only single-agent chemotherapy (cisplatin), and the study arm was given two drugs (cisplatin and gemcitabine) during CCRT. We determined this to show high risk of bias, as it is likely to have had a significant effect on the outcomes.

Effects of interventions

We were unable to pool data because one of the included trials ([Dueñas-González 2011](#)) used different interventions during CCRT between the two arms (study arm received a combination of gemcitabine and cisplatin; control arm received cisplatin alone). In addition, different types of ACT were used in the two included studies; one trial used 5-fluorouracil (5-FU) ([Lorvidhaya 2003](#)), and the other ([Dueñas-González 2011](#)) used a combination of gemcitabine and cisplatin.

Survival

[Lorvidhaya 2003](#) found no benefit for ACT over CCRT alone. Using the Parmar method to estimate hazard ratio, we found that

the HR for OS was 1.309 (95% confidence interval (CI) 0.795 to 2.157) and for DFS was 1.125 (95% CI 0.799 to 1.586) among participants who received adjuvant chemotherapy (ACT).

[Dueñas-González 2011](#) showed significant improvement in PFS and OS among those who received CCRT plus ACT compared with those given CCRT alone (HR 0.68, 95% CI 0.49 to 0.95 for PFS, P value 0.027; HR 0.68, 95% CI 0.49 to 0.95 for OS, P value 0.022). The benefit of ACT was demonstrated in all subgroups. Subsequent analyses ([Dueñas-González 2012](#)) showed that benefit from ACT, PFS in particular, was greater in women with more

advanced disease, larger tumour size and age younger than 55 years. The hazard ratio of PFS among participants with stage III to IVA disease who were given CCRT and ACT compared with those who received only CCRT was 0.59 (95% CI 0.37 to 0.97, P value 0.036).

Data on survival from both studies are summarised in Additional tables: [Table 1](#).

No meta-analysis was performed. Data on progression-free survival for each individual trial are shown in [Figure 2](#) and on overall survival in [Figure 3](#).

Figure 2. Forest plot of comparison: I Survival, outcome: I.1 Progression-free survival.

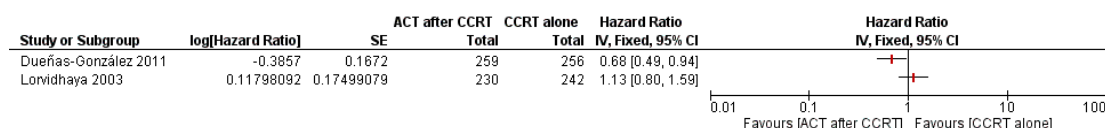
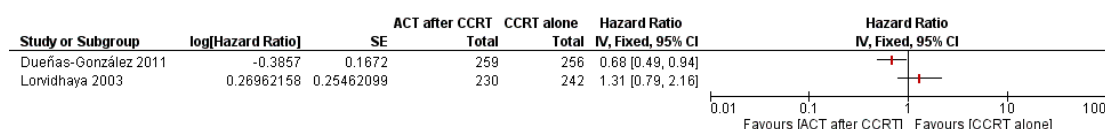


Figure 3. Forest plot of comparison: I Survival, outcome: I.2 Overall survival.



Failure after treatment

[Lorvidhaya 2003](#) did not demonstrate that the addition of chemotherapy could decrease total failure rate or loco-regional or distant failure after CCRT. Total failure rates were 29.0% among participants who received CCRT (arm 3), and 31.2% among those given CCRT plus ACT (arm 4). No significant differences in loco-regional or distant recurrence were noted among participants who were treated with CCRT alone or CCRT plus ACT: 14.3% versus 17.6% (P value not given) for local recurrence, and 17.7% versus 19.5% (P value not given) in arm 3 and arm 4, respectively.

Rates of local failure in [Dueñas-González 2011](#) were not different

(11.2% versus 16.4%, P value 0.097). However, distant failure rate was lower in the ACT group: 8.1% versus 16.4% (P value 0.005). Differences in chemotherapy during CCRT should be noted; it is not possible to determine whether differences were due to ACT given alone.

Data on recurrences from both studies are summarised in Additional tables: [Table 2](#).

No meta-analysis was performed. Data on treatment failure at all sites for each individual trial are shown in [Analysis 2.1](#) ([Figure 4](#)), local failure in [Analysis 2.2](#) ([Figure 5](#)) and distant failure in [Analysis 2.3](#) ([Figure 6](#)).

Figure 4. Forest plot of comparison: 2 Failure after treatment, outcome: 2.1 Total failure after treatment.

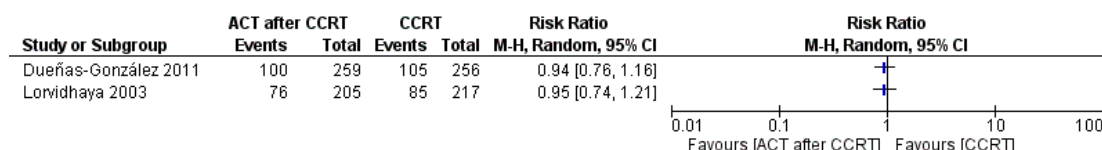


Figure 5. Forest plot of comparison: 2 Failure after treatment, outcome: 2.2 Local failure.

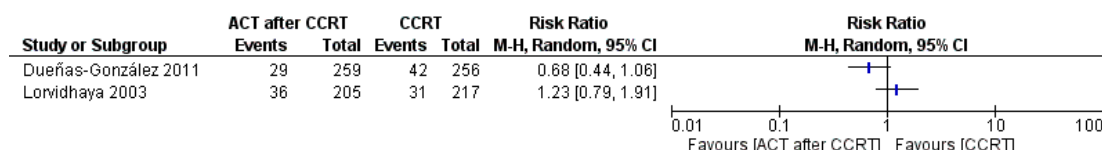
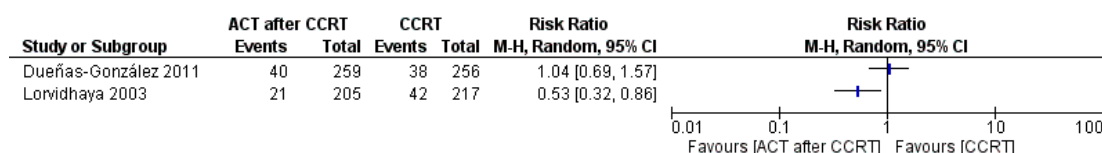


Figure 6. Forest plot of comparison: 2 Failure after treatment, outcome: 2.3 Distant failure.



Response rate

Only [Dueñas-González 2011](#) reported response rates in the two treatment arms. These did not differ (95.8% in the CCRT plus ACT arm versus 93.4% in the CCRT arm, P value 0.249) (Additional tables: [Table 3](#)). No information on response rates was available for [Lorvidhaya 2003](#).

Adverse events

[Lorvidhaya 2003](#) reported that one participant in the CCRT arm died from persistent thrombocytopenia and leucopenia. Gastrointestinal symptoms were greater in the CCRT arm, but study authors stated that most women tolerated the treatment well (actual numbers not given). Haematological toxicities were not increased by ACT after CCRT. Anaemia of grade 2 was 24.2% among participants given CCRT plus ACT and 20.6% in those treated with only CCRT. Respective grade 3 and 4 leucopenia was 2.9% and 4.1%, and grade 3 and 4 thrombocytopenia was 1.5% and 2.3%

(Additional tables: [Table 4](#)). No differences in late side effects were observed among studied arms (Additional tables: [Table 5](#)).

[Dueñas-González 2011](#) reported detailed toxicities in both treatment arms. It should be noted that chemotherapy during CCRT differed when added to ACT. More women who had CCRT plus ACT were hospitalised: 30 women versus 11 who had CCRT only (P value 0.003). Women who received CCRT plus ACT also had a greater number of grade 3 or 4 overall toxicities (87.0% vs 46.0%, P value < 0.001). Rates of grade 3 and 4 toxicities in women who received CCRT and ACT versus CCRT alone were 71.9% versus 23.9% for haematological and 34.6% versus 10.6% for gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain/cramping, anorexia and proctitis), respectively. More women in the study arm had received one or more blood transfusions: 49.2% versus 27.5% (P value < 0.001). Overall, three deaths occurred in the CCRT plus ACT arm during or 30 days after treatment. Two deaths were attributed to the ACT. When study authors assessed toxicities from the preadjuvant and adjuvant treatments separately,

they found that the CCRT plus ACT arm had greater toxicity than the CCRT alone arm during the preadjuvant phase. However, the incidence of new toxicity during ACT was generally low. No meta-analysis was performed. Data on anaemia and thrombocytopenia from each individual study are shown in [Analysis 3.1](#) (Figure 7) and Figure 8, respectively.

Figure 7. Forest plot of comparison: 3 Adverse events, outcome: 3.1 Anaemia.

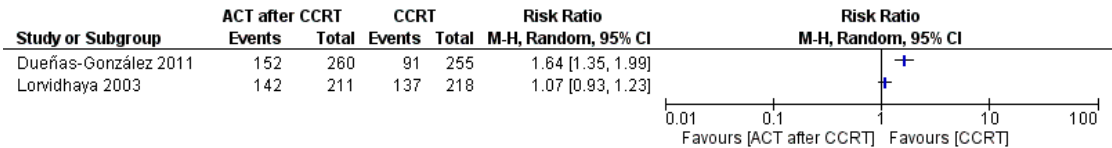
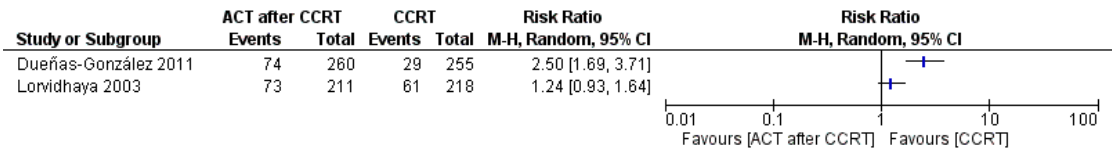


Figure 8. Forest plot of comparison: 3 Adverse events, outcome: 3.2 Thrombocytopenia.



Other outcomes

No information on QoL was reported in either study ([Dueñas-González 2011](#); [Lorvidhaya 2003](#)).

DISCUSSION

Summary of main results

Results from the two studies were not amenable to meta-analysis for evaluation of the effect of adjuvant chemotherapy (ACT) after concurrent chemoradiation therapy (CCRT) in terms of survival and total failure rate after treatment.

Overall completeness and applicability of evidence

Two studies met the inclusion criteria ([Dueñas-González 2011](#); [Lorvidhaya 2003](#)). We observed important differences between

the two studies, which did not allow us to perform a meta-analysis to address all the objectives as planned.

The studies were conducted in the 1990s and 2000s. This resulted in different trial designs as the computed tomography (CT) scanner was not used consistently as an investigative tool. Although CT scan has never been included in the International Federation of Gynecology and Obstetrics (FIGO) staging process, it is used routinely and impacts treatment decisions in clinical practice and modern research settings. [Lorvidhaya 2003](#) conducted their study from 1988 to 1994, when CT scan of the abdomen was not routinely practiced. This may have led to heterogeneous participant characteristics or risk features. Some participants with locally advanced cervical cancer (LACC) may already have had distant disease beyond the pelvis, particularly the para-aortic lymph nodes. This could affect the incidence and detection of systemic failure, as standard physical examination and plain film chest imaging during follow-up may not detect subtle disease, especially in retroperitoneal nodes. This is likely to affect the progression-free period. [Dueñas-González 2011](#), who conducted their study from 2002 to 2004, included CT scanning in all participants as an evaluation

tool and excluded cases with para-aortic lymph node metastasis. This is likely to have resulted in a different participant cohort than was seen in the [Lorvidhaya 2003](#) study, with reduced risk of failure after treatment. CT scanning was also used during surveillance and is likely to have detected recurrence earlier than standard evaluation. This tended to reduce the progression-free interval compared with clinical follow-up.

The second difference was the chemotherapy used in each study. [Lorvidhaya 2003](#) used non-platinum drugs in their study, and [Dueñas-González 2011](#) used platinum-based chemotherapy, which is the current standard of care.

Given these differences, it was believed inappropriate to perform a meta-analysis of data extracted from the two studies.

Quality of the evidence

Evidence from our review neither supports nor refutes the use of adjuvant chemotherapy to improve survival outcomes or to decrease failure after treatment. Some issues, which were observed in each trial as detailed below, were considered 'flaws' that prevented a definitive conclusion.

Oral adjuvant chemotherapy was used in [Lorvidhaya 2003](#) (oral 5-FU) post combination with mitomycin during CCRT. This study did not report measures used to ascertain participant compliance. This might be reflected by similar rates of toxicity among participants who received or did not receive ACT after CCRT. These factors may have decreased the potential activity of ACT. [Dueñas-González 2011](#) described an imbalance in chemotherapy concurrent with radiation therapy between the two study arms. Single-agent cisplatin was given to participants in the control arm, whereas cisplatin and gemcitabine were given to participants in the study arm. The combined drug was also given as ACT in the study arm. Hence, it is not possible to attribute any survival advantage in the study arm to ACT alone, as this may be due to the effects of more chemotherapy during CCRT rather than to the effects of ACT.

The other issue was the means of tumour assessment. All participants in [Lorvidhaya 2003](#) underwent only chest x-ray and intravenous pyelography, as allowed by the FIGO staging system. Computed tomography scan was not required. This is likely to have contributed to heterogeneous participant characteristics com-

pared with those in [Dueñas-González 2011](#), because some women may already have had systemic spread of disease before treatment. All women in [Dueñas-González 2011](#) underwent whole abdominal CT scanning as part of the baseline evaluation and post-treatment follow-up. This was done to assess the para-aortic lymph nodes, and women with confirmed nodal involvement (confirmed by fine-needle aspiration) were excluded. This is likely to have decreased any bias due to imbalance between the two arms, as only participants without proven preexisting systemic spread were included.

Regarding the other outcomes, numbers of local and systemic failures and limited aspects of toxicity (anaemia and thrombocytopenia) were consistently reported in both studies ([Dueñas-González 2011](#); [Lorvidhaya 2003](#)). However, we determined that the results were inconclusive because substantial heterogeneity was observed in the analyses.

The last observation was the duration of follow-up in both studies, which was relatively short, so outcomes from long-term follow-up are necessary.

Potential biases in the review process

The authors of this review, with support from the Cochrane Gynaecological Cancer Group, performed a comprehensive search. All studies were sifted and data were extracted by two review authors independently. Only RCTs were included in this review, as they provide the best available evidence. RCTs conducted when CCRT was not used as standard treatment for LACC with only radiation therapy used in the control arm ([Kantardzic 2004](#); [Vishnevskaja 1999](#); [Wang 2010](#); [Wong 1999](#)) or in both arms ([Chiara 1994](#)) were excluded because radiation alone at present is considered suboptimal standard treatment for patients with LACC. Data from the study arms of these studies ([Kantardzic 2004](#); [Vishnevskaja 1999](#); [Wang 2010](#); [Wong 1999](#)) or from both arms ([Chiara 1994](#)), using CCRT plus ACT, were not reported. Randomised controlled trials using other treatment (e.g. neoadjuvant chemotherapy) in addition to CCRT and ACT were also excluded because this treatment approach may obviate the effects of ACT. No other potential biases were noted in the review process. The review authors' judgements about each risk of bias item for each included study are shown in [Figure 9](#) and [Figure 10](#).

Figure 9. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

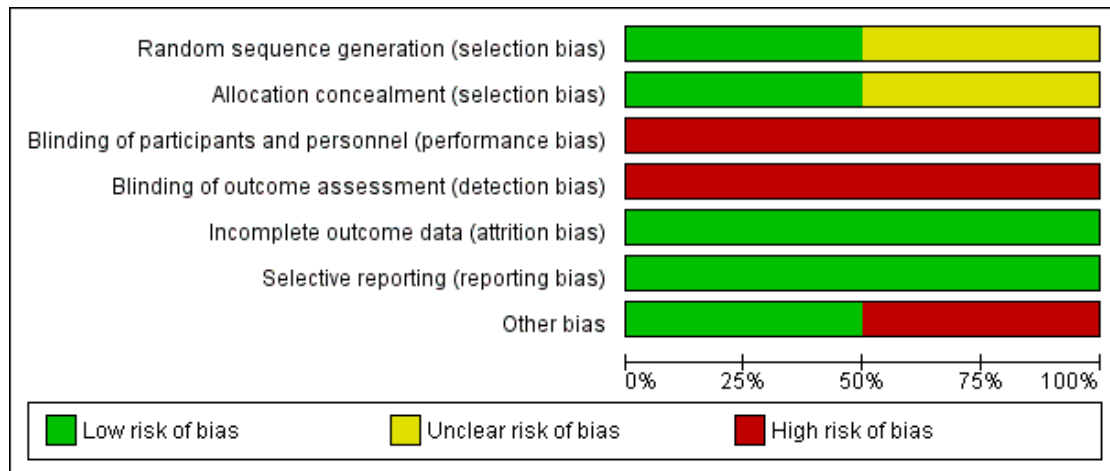
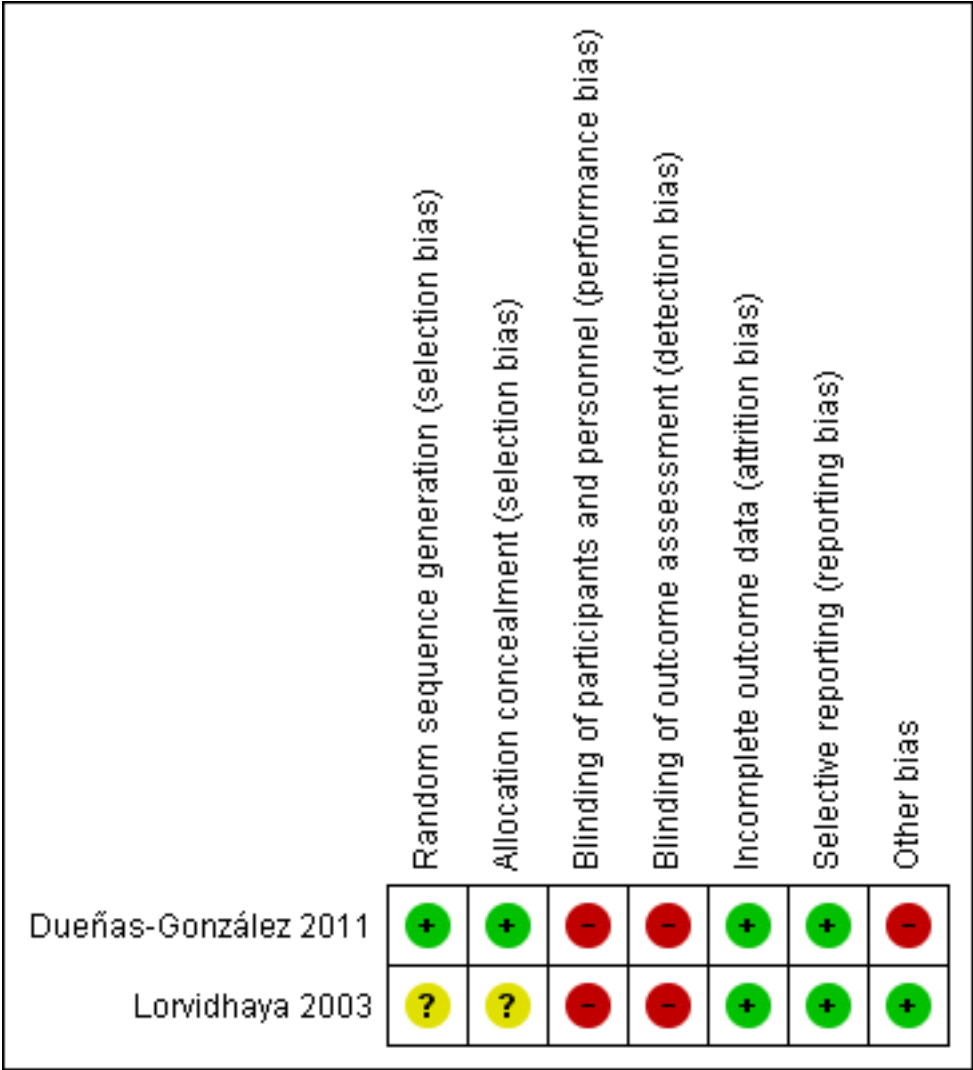


Figure 10. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Agreements and disagreements with other studies or reviews

One of the authors of this review performed a narrative review (Tangjitgamol 2011) on this topic, including three prospective single-arm studies (Choi 2007; Vrdoljak 2006; Zhang 2010), one matched-case comparison (Choi 2010) and four RCTs (Dueñas-González 2011; Kantardzic 2004; Lorvidhaya 2003; Wong 1999). Most of these studies were excluded from our review for reasons stated in the section on Characteristics of excluded studies.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence is insufficient to support the use of ACT after standard CCRT outside of clinical trials.

Implications for research

Along with standard CCRT, alternative or additional treatments are required for patients with LACC to improve survival outcomes. Very few trials have explored this topic, so additional research,

focused on the role of adjuvant chemotherapy after standard concurrent chemoradiation, is required. Future studies should aim to ensure balance in treatments given before ACT and to exclude participants with evidence of distant disease by using appropriate imaging modalities (CT scan, positron emission tomography (PET) CT, etc).

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The views and opinions expressed therein are those of the review authors and do not necessarily reflect those of the NIHR, the National Health Service (NHS) or the Department of Health.

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Tangjitgamol 2011

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Dueñas-González 2011

Methods	Multi-centre randomised international controlled trial in 8 countries: Argentina, Bosnia and Herzegovina, India, Mexico, Pakistan, Panama, Peru and Thailand. Stratified randomisation was done by using the Pocock and Simon algorithm according to disease stage (IIB versus III to IVA), tumour diameter (< versus ≥ 5 cm), investigational centre, radiation equipment (cobalt-60 versus linear accelerator) and participant age (< versus ≥ 55 years)	
Participants	515 eligible participants 18 to 70 years of age who had: • cervical cancer stage IIB to IVA • Karnofsky performance score ≥ 70 • tumours of squamous cell carcinoma, adenocarcinoma, adeno/squamous carcinoma and poorly differentiated carcinoma • no enlarged para-aortic lymph node > 1 cm that was proven on fine-needle enlargement to show metastatic cancer • normal complete blood count and renal function	
Interventions	Arm A-CCRT plus ACT: 259 participants with mean age of 45 years • Cisplatin 40 mg/m² by IV infusion over 60 minutes, followed immediately by gemcitabine 125 mg/m² administered by IV infusion once weekly for 6 weeks as concurrent chemotherapy with radiation. Adjuvant chemotherapy given 2 weeks after brachytherapy was cisplatin 50 mg/m² on day 1 and gemcitabine 1000 mg/m² on days 1 and 8 for 2 consecutive 21-day cycles Arm B-CCRT alone: 256 participants with mean age of 46 years • Single-agent cisplatin 40 mg/m² by IV infusion once weekly for 6 weeks as concurrent chemotherapy with radiation	
Outcomes	Primary endpoint: progression-free survival (PFS) at 3 years Secondary efficacy measures: overall survival (OS), time to progressive disease (TtPD), TRR, local failure rate (LFR), clinical adverse events (AEs)	
Notes	All participants had whole abdominal CT scan as part of baseline evaluation and post-treatment follow-up. This was used to assess the para-aortic lymph node and was to be excluded in the presence of metastasis confirmed by FNA	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation was generated by central telephone of the pharmaceutical company providing research funding (Eli Lilly, Indianapolis, IN, USA)

Allocation concealment (selection bias)	Low risk	Participants were randomly assigned using the Pocock and Simon algorithm according to disease stage (IIB versus III to IVA), tumour diameter (< versus $\geq$ 5 cm), investigational centre, radiation equipment (cobalt-60 versus linear accelerator) and participant age (< versus $\geq$ 55 years) Allocation was concealed until interventions were assigned
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was performed during treatment because of the nature of the intervention. No information was provided on the blinding process during follow-up or surveillance
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were objective findings and were clearly defined in the trial but were not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	After a median follow-up period of 46.9 months, a total of 56 participants (approximately 11%) were lost to follow-up by the end of the study. Reasons for loss to follow-up were similar in the 2 treatment arms
Selective reporting (reporting bias)	Low risk	Although the primary endpoint was changed from OS to PFS after completion of enrolment, all outcomes specified in the protocol were reported
Other bias	High risk	No imbalance between baseline characteristics was observed in the 2 arms. However, chemotherapy schedules in the CCRT phase are also different, and this is likely to have had a major bearing on study results

Lorvidhaya 2003

Methods	Multi-centre randomised controlled trial
Participants	926 eligible participants younger than 65 years of age who had: • cervical cancer with stage IIB, III, IVA (particularly for stage IIB, the central tumour must be larger than 3 cm and/or must have involved more than half of the parametrium) • squamous cell carcinoma, adenocarcinoma or adenosquamous cell carcinoma histopathology • performance status < or = to 2 according to the Eastern Cooperative Oncology

	Group normal complete blood count and renal function	
Interventions	4 arms of treatment: arm 1-RT only; arm 2-RT plus ACT; arm 3-CCRT; arm 4-CCRT plus ACT Note: - Only data from arm 3 (233 participants with mean age of 48 years) and arm 4 data (230 participants with mean age of 50 years) were extracted and used in this review - Chemotherapy given concurrently with RT (arm 3 and arm 4) consisted of mitomycin C 10 mg/m² IV days 1 and 29 plus oral 5-FU 300 mg/d on days 1 to 14 and 29 to 42 in the first 673 participants, then 5 days per week during radiation in subsequent participants 3. Adjuvant chemotherapy given (arm 2 and arm 4) was oral 5-FU 200 mg/d for 3 courses (given 4 weeks with a 2-week rest every 6 weeks)	
Outcomes	Overall survival and progression-free survival	
Notes	All participants had only chest-x ray and intravenous pyelography, as allowed in the FIGO staging system. CT scan was not performed in all participants	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was stratified according to each individual centre of the six participating centres. Method and the centre or site responsible for randomisation were not detailed
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding during treatment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were objective findings and were clearly defined in the trial but were not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	13 participants with small cell carcinoma (6 in the CCRT group and 7 in the CCRT plus ACT group; approximately 3% both) were excluded from the analysis - After a median follow-up of 89 months, 12 (5%) and 19 (8%) of the participants in both arms were lost to follow-up and received incomplete

		treatment. Reasons were not specified. Participants were censored as having failure of treatment
Selective reporting (reporting bias)	Low risk	PFS and OS were reported according to the protocol
Other bias	Low risk	No imbalance in baseline characteristics between the 2 arms was noted

ACT: adjuvant chemotherapy.

AE: adverse event.

CCRT: concurrent chemoradiation therapy.

CT: computed tomography.

FIGO: International Federation of Gynecology and Obstetrics.

FNA: fine-needle aspiration.

LFR: local failure rate.

OS: overall survival.

PFS: progression-free survival.

RT: radiation therapy.

TtPD: time to progressive disease.

Characteristics of excluded studies [author-defined order]

Study	Reason for exclusion
Chiara 1994	This trial randomly assigned 64 participants with stage IIB to III cervical cancer to receive RT alone as control arm or sequential chemotherapy (biweekly cisplatin) given 2 cycles before and 4 cycles after RT in the study arm. It was excluded because (1) In addition to ACT, the drug was given before RT as neoadjuvant chemotherapy in the study arm; and (2) standard treatment in both arms was only RT (not CCRT)
Choi 2007	This phase II study treated 30 participants with cervical carcinoma of FIGO stage IB2 to IVA with CCRT (cisplatin and 5-FU) followed by 3 more cycles of the same chemotherapy. It was excluded because it was a single-arm study without a comparative group
Choi 2010	This prospective study included 78 participants with stage IIB to IVA cervical cancer. The control arm received only CCRT (tri-weekly cisplatin and 5-FU or weekly cisplatin). The study arm received the same CCRT followed by chemotherapy (either 3 tri-weekly cisplatin and 5-FU or 6 weekly cisplatin). It was excluded because it was a matched-case comparison study without randomisation
Domingo 2009	This prospective study included 60 participants with stage IIB to IIIB cervical cancer who received CCRT (capecitabine) followed by ACT (same drug but increased dose) for 6 more cycles. It was excluded because it was a single-arm phase II study without a comparator group

(Continued)

Kantardzic 2004	This trial randomly assigned 80 participants with stage IIB to III cervical cancer to RT alone or CCRT (cisplatin and bleomycin) followed by additional cycles of the same chemotherapy. It was excluded because only RT was given in the control arm
Kim 2012	This prospective study evaluated the efficacy and toxicity of consolidation chemotherapy (paclitaxel and carboplatin) after CCRT in 35 participants with stage IB1 to IVA cervical cancer. It was excluded because (1) It was a phase II study without randomisation; (2) different stages and primary treatment were given to participants in each group (group 1 comprised 19 participants with stage IB1 to IIA cervical cancer who had risk factors identified from surgery and received adjuvant CCRT, and group 2 consisted of 18 participants with stage IIB to IVA cervical cancer who received CCRT); and (3) all participants with cervical cancer in both groups, who received 3 cycles of consolidation chemotherapy
Mahasittiwat 2011	This prospective study included 19 participants with cervical carcinoma of FIGO stage IIB and IIIB who received CCRT. Only 9 received 3 cycles of consolidation chemotherapy (cisplatin and ifosfamide). It was excluded because it was a phase II single-arm study without a comparator group
McCaffrey 2011	This phase II study evaluated the activity of a 4-drug regimen of chemotherapy (cisplatin, bleomycin, methotrexate and 5-FU) in 67 participants with cervical cancer stage IB to IIIB. It was excluded because (1) it was a phase II study without randomisation; (2) participants were selected to have different primary and adjuvant treatment according to their clinical features (one group (42 participants) received neoadjuvant chemotherapy before surgery and consolidated with RT; the other group (25 participants) had primary surgery followed by ACT (and optional radiation) if pathological risk factors were identified); and (3) The primary treatment in both groups was not CCRT
Tang 2012	This trial randomly assigned 880 participants with cervical cancer stage IIB to IVA of adenocarcinoma histology to received CCRT as the control arm or 1 cycle of neoadjuvant chemotherapy (paclitaxel and cisplatin) followed by CCRT (cisplatin or cisplatin and 5-FU) and 2 cycles of consolidation chemotherapy with the same drugs as the study arm. This study was excluded because neoadjuvant chemotherapy was given along with additional chemotherapy after CCRT
Vishnevskiaia 1999	This trial randomly assigned 100 participants with locally advanced cervical carcinoma to the control arm to receive only RT or to the study arm to receive multi-modality treatment, including immunotherapy (epithalamin), neoadjuvant chemotherapy (cisplatin and 5-FU) and CCRT followed by ACT (multiple drugs). It was excluded because (1) the study arm received neoadjuvant chemotherapy along with CCRT and ACT; and (2) the control arm did not receive CCRT-only RT
Vrdoljak 2006	This prospective study included 62 participants with stage IB2 to IVA cervical cancer who received CCRT (cisplatin and ifosfamide) followed by consolidation chemotherapy (same drug). It was excluded because it was a single-arm study without a comparator arm
Wang 2010	This trial randomly assigned 156 participants with stage IIa to IIIB cervical squamous cell carcinoma to receive RT alone or CCRT (weekly cisplatin) followed by 3 cycles of ACT (docetaxel and cisplatin). It was excluded because only RT was given in the control arm
Wong 1999	This trial randomly assigned 220 participants with bulky stage I, II and III cervical cancer to receive standard pelvic RT or CCRT (epirubicin) followed by 5 additional cycles of the same chemotherapy. It was excluded because only RT was given in the control arm

(Continued)

Zhang 2010	This prospective study included 34 participants with stage IIB to IIIB cervical cancer, who received CCRT (paclitaxel and nedaplatin) followed by 4 additional cycles of consolidation chemotherapy (same drug). It was excluded because it was a single-arm study without a comparator control arm
Vrdoljak 2005	This was a preliminary report of a single-arm prospective study by Vrdoljak et al, which described findings in 44 out of 62 total participants with stage IB2 to IVA cervical cancer, who received CCRT (cisplatin and ifosfamide) followed by consolidation chemotherapy (same drug)

5-FU: 5-Fluorouracil

ACT: adjuvant chemotherapy

CCRT: concurrent chemoradiation therapy

FIGO: International Federation of Gynecology and Obstetrics

RT: radiation therapy

Characteristics of ongoing studies [ordered by study ID]

Mileshkin 2010

Trial name or title	A phase III trial of adjuvant chemotherapy following chemoradiation as primary treatment for patients with locally advanced cervical cancer compared with chemoradiation alone: the outback trial
Methods	A randomised controlled multi-centre clinical trial (ANZGOG 0902/GOG-0274/RTOG 1174)
Participants	780 participants with locally advanced cervical cancer suitable for primary treatment with chemoradiation. Histologically confirmed diagnosis of squamous cell carcinoma, adenocarcinoma or adenosquamous cell carcinoma of the cervix with stage IB1 and positive nodes, IB2, II, IIIB or IVA disease. Participants must have received no previous pelvic radiotherapy or chemotherapy for this tumour and must not have needed interstitial brachytherapy treatment at presentation
Interventions	Participants are randomly assigned to 2 groups. All participants receive cisplatin weekly for 6 weeks concurrent with pelvic radiation followed by observation in the control arm or an additional 4 cycles of chemotherapy (paclitaxel and carboplatin every 3 weeks) in the study arm
Outcomes	Progression-free survival, overall survival, adverse events, prognostic biomarkers
Starting date	2/22/2012
Contact information	outback@ctc.usyd.edu.au
Notes	

Tangjitgamol 2014

Trial name or title	Randomised controlled trial comparing concurrent chemoradiation versus concurrent chemoradiation followed by adjuvant chemotherapy in patients with locally advanced cervical cancer
Methods	Randomised controlled multi-centre trial (TCTR 20140106001)
Participants	500 participants with locally advanced cervical cancer (FIGO stage IIB to IVA). Histologically confirmed diagnosis of squamous cell carcinoma, adenocarcinoma or adenosquamous cell carcinoma of the cervix. Participants must have ECOG performance score of 0 to 2 and adequate bone marrow, liver and renal function. Participants with suspicious para-aortic lymph node metastasis, presence of adnexal mass or chronic illness (e.g. renal impairment, neuropathy, immunosuppressive disorders) will be excluded
Interventions	Participants are randomly assigned to 2 arms. After receiving concurrent pelvic radiation and cisplatin weekly for 6 weeks, the control arm will be observed, while the study arm will receive 3 cycles of paclitaxel and carboplatin every 4 weeks
Outcomes	Progression-free survival, overall survival, response rate, cost-utility analysis
Starting date	January 2014
Contact information	siriwanonco@yahoo.com
Notes	

ECOG: Eastern Cooperative Oncology Group.

FIGO: International Federation of Gynecology and Obstetrics.

DATA AND ANALYSES

Comparison 1. Survival

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Progression-free survival	2		Hazard Ratio (Fixed, 95% CI)	Totals not selected
2 Overall survival	2		Hazard Ratio (Fixed, 95% CI)	Totals not selected

Comparison 2. Failure after treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total failure after treatment	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Local failure	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Distant failure	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 3. Adverse events

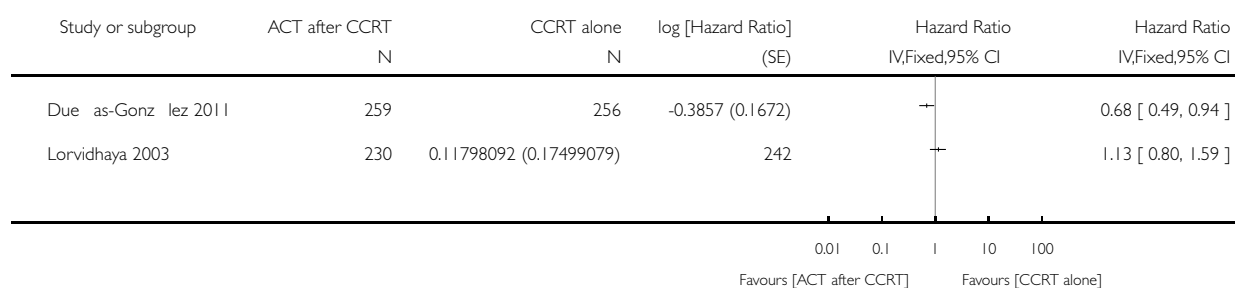
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Anaemia	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Thrombocytopenia	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Survival, Outcome 1 Progression-free survival.

Review: Adjuvant chemotherapy after concurrent chemoradiation for locally advanced cervical cancer

Comparison: 1 Survival

Outcome: 1 Progression-free survival

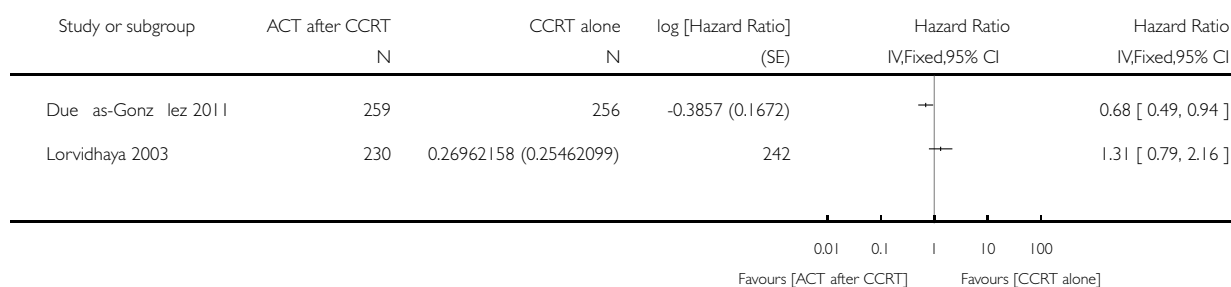


Analysis 1.2. Comparison 1 Survival, Outcome 2 Overall survival.

Review: Adjuvant chemotherapy after concurrent chemoradiation for locally advanced cervical cancer

Comparison: 1 Survival

Outcome: 2 Overall survival

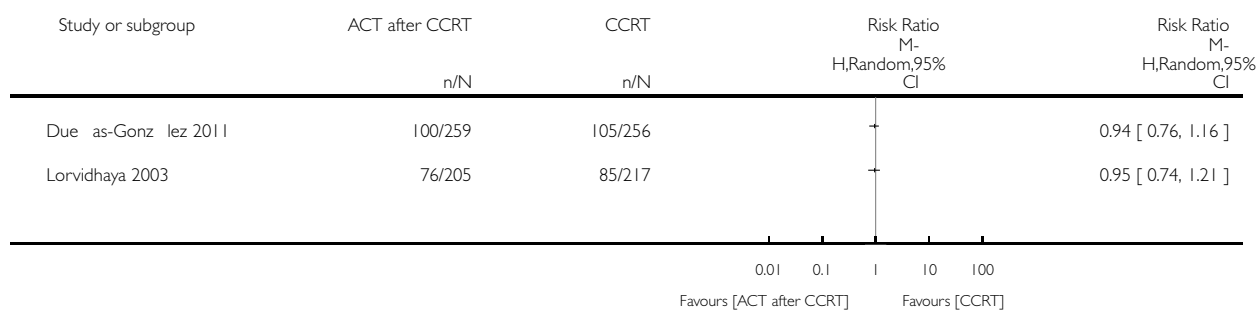


Analysis 2.1. Comparison 2 Failure after treatment, Outcome 1 Total failure after treatment.

Review: Adjuvant chemotherapy after concurrent chemoradiation for locally advanced cervical cancer

Comparison: 2 Failure after treatment

Outcome: 1 Total failure after treatment

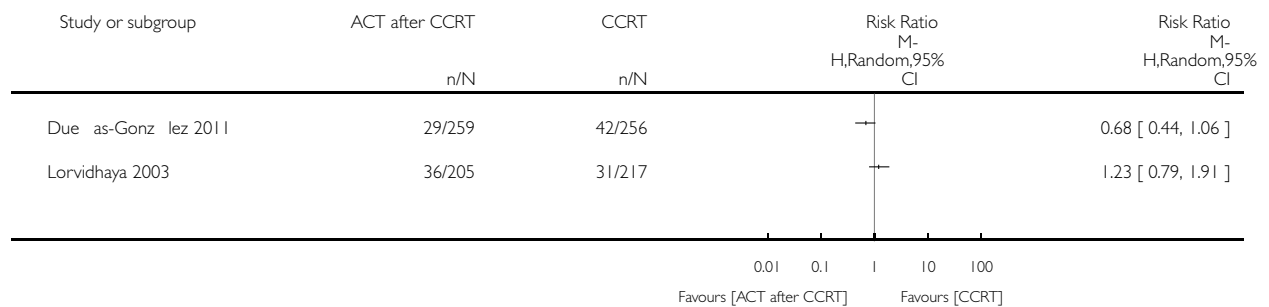


Analysis 2.2. Comparison 2 Failure after treatment, Outcome 2 Local failure.

Review: Adjuvant chemotherapy after concurrent chemoradiation for locally advanced cervical cancer

Comparison: 2 Failure after treatment

Outcome: 2 Local failure

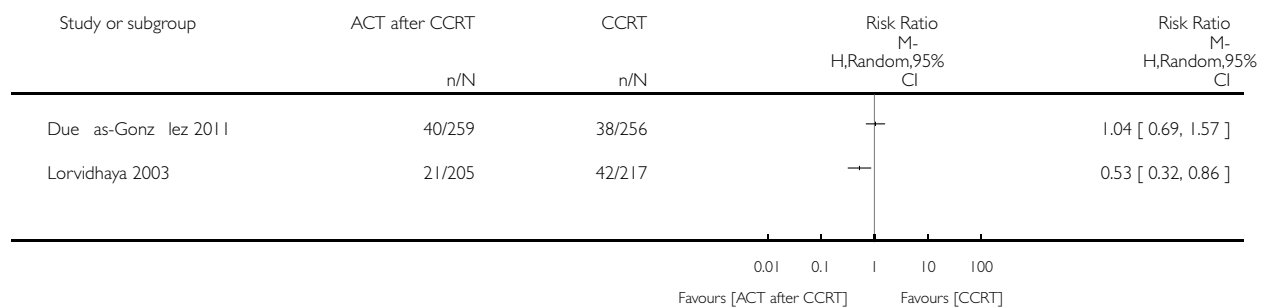


Analysis 2.3. Comparison 2 Failure after treatment, Outcome 3 Distant failure.

Review: Adjuvant chemotherapy after concurrent chemoradiation for locally advanced cervical cancer

Comparison: 2 Failure after treatment

Outcome: 3 Distant failure

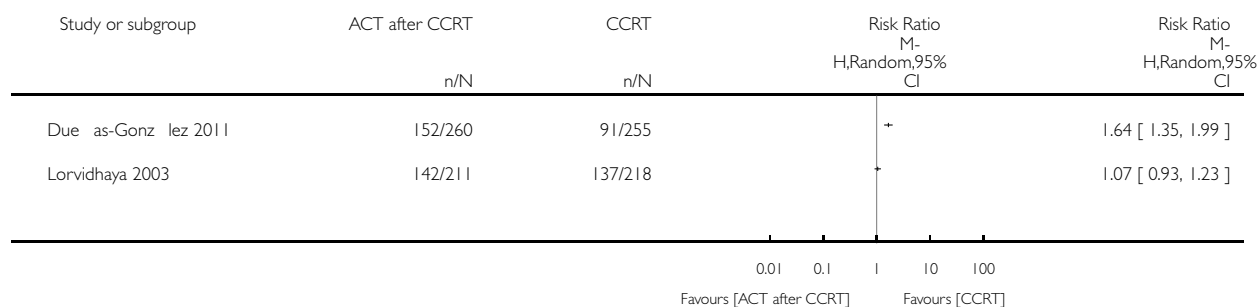


Analysis 3.1. Comparison 3 Adverse events, Outcome 1 Anaemia.

Review: Adjuvant chemotherapy after concurrent chemoradiation for locally advanced cervical cancer

Comparison: 3 Adverse events

Outcome: 1 Anaemia

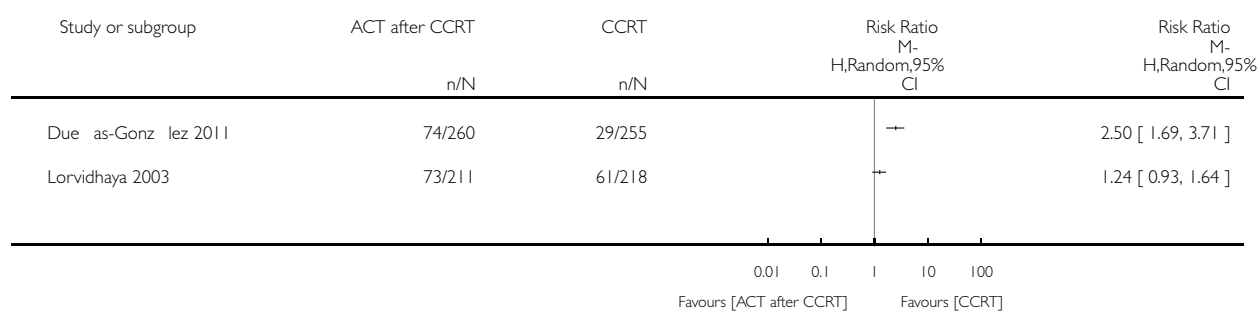


Analysis 3.2. Comparison 3 Adverse events, Outcome 2 Thrombocytopenia.

Review: Adjuvant chemotherapy after concurrent chemoradiation for locally advanced cervical cancer

Comparison: 3 Adverse events

Outcome: 2 Thrombocytopenia



ADDITIONAL TABLES

Table 1. Survival outcome

Study	Lordvithaya	Dueñas-Gonzalez
N (CCRT versus CCRT/ACT)	233 versus 230	256 versus 259
FU	89 months	46.9 months
Outcomes (CCRT versus CCRT/ACT)		
1. OS		
· 3-year OS	85% versus 79% (estimated from graph), P value NS HR 1.309, 95% CI 0.795 to 2.157 (by Parmar method)	69% versus 78% (estimated from graph) HR 0.68, 95% CI 0.49 to 0.95, P value 0.0224
· 5-year OS	82.7% (79.0 to 86.4) versus 73.6 (67.1 to 80.1), P value NS	-
2. PFS		
· 3-year PFS	68% versus 63% (estimated from graph), P value NS HR 1.125, 95% CI 0.799 to 1.586 (by Parmar method)	65.0% (58.5 to 70.7) versus 74.4 % (68 to 79.8) HR 0.68, 95% CI 0.49 to 0.95), P value 0.0227
· 5-year PFS	64.5% (60.6 to 68.0) versus 59.7% (53.6 to 65.8), P value NS	-

Table 2. Recurrence

Study	Lordvithaya	Dueñas-Gonzalez
N (CCRT versus CCRT/ ACT)	233 versus 230	256 versus 259
· Local (with or without DR)	31 (14.3%) versus 36 (17.6%), P value NS	16.4% versus 11.2%, P value 0.097
· Distant (with or without LR)	38 (17.7%) versus 40 (19.5%), P value NS	16.4% versus 8.1%, P value 0.005
· Local and/ or distant	63 (29.0%) versus 64 (31.2%), P value NS	-

Table 3. Response rate

Study	Lordvithaya	Dueñas-Gonzalez
Response rate	NA	93.4 (89.6 to 96.1) in CCRT arm versus 95.8 (92.5 to 97.9) in CCRT + ACT arm, P value 0.249

Table 4. Acute adverse event

Adverse events/Study	Lordvithaya n (%)		Dueñas-Gonzalez n (%)	
	CCRT (N = 218)	CCRT + ACT (N = 211)	CCRT (N = 255)	CCRT + ACT (N = 260)
Acute adverse event (grade 1 to 2)				
1. Haematological				
• Leucopenia	110 (50.4)	139 (65.8)	NA	
• Anaemia	137 (62.8)	142 (67.3)	86 (33.8)	128 (49.3)
• Neutropenia	NA		62 (24.3)	80 (30.8)
• Febrile neutropenia	NA		0	1 (0.4)
• Thrombocytopenia	56 (25.7)	70 (33.5)	26 (10.2)	58 (32.4)
• Haemorrhage	NA		NA	
2. Gastrointestinal				
• Nausea	NA		148 (58.0)	153 (58.8)
• Vomiting	NA		116 (45.5)	129 (49.6)
• Anorexia	NA		37 (14.5)	46 (17.7)
• Diarrhoea	NA		119 (46.7)	121 (46.5)
• Liver	NA		6 (1.6)	33 (12.6)
• Proctitis	NA		20 (7.9)	29 (11.2)
3. Genitourinary (increased Cr level)	NA		2 (0.8)	5 (1.9)

Table 4. Acute adverse event (Continued)

4. Skin	NA		40 (15.7)	45 (17.3)
5. Neurological	NA		NA	
6. Pulmonary	NA		NA	
Acute adverse event (grade 3 to 4)				
1. Haematological				
• Leucopenia	9 (4.1)	6 (2.9)	NA	
• Anaemia	0		5 (2.0)	24 (9.2)
• Neutropenia	NA		15 (5.9)	133 (51.2)
• Febrile neutropenia	NA		1 (0.4)	6 (2.3)
• Thrombocytopenia	5 (2.3)	3 (1.5)	3 (1.2)	16 (6.2)
• Haemorrhage	NA		NA	
2. Gastrointestinal				
• Nausea	NA		7 (2.7)	11 (4.2)
• Vomiting	NA		7 (2.8)	20 (7.7)
• Anorexia	NA		0	1 (0.4)
• Diarrhoea	NA		12 (4.7)	46 (17.7)
• Liver	NA		0	4 (1.6)
• proctitis	NA		1 (0.4)	9 (3.5)
3. Genitourinary (in- creased Cr level)	NA		2 (0.8)	4 (1.5)
4. Skin	NA		27 (10.6)	29 (11.2)
5. Neurological	NA		NA	
6. Pulmonary	NA		NA	

Table 5. Late adverse event

Study	Lordvithaya n (%)	Dueñas-Gonzalez n (%)
Late adverse event (grade 3 to 4)		
1. Bowel	3.1% vs 5.8%	1 (0.5) vs 5 (2.3)
2. Bladder		1 (0.5) vs 3 (1.4)
3. Mucous membrane	NA	1 (0.5%) vs 1 (0.5)
4. Subcutaneous		0 vs 1 (0.5)

APPENDICES

Appendix 1. CENTRAL

- #1 MeSH descriptor: [Uterine Cervical Neoplasms] this term only
- #2 (cervi* near/5 (cancer* or neoplas* or carcinoma* or tumor* or tumour* or malignan*))
- #3 #1 or #2
- #4 Any MeSH descriptor with qualifier(s): [Radiotherapy - RT]
- #5 MeSH descriptor: [Radiotherapy] explode all trees
- #6 MeSH descriptor: [Chemoradiotherapy] explode all trees
- #7 (radiotherap* or radiat* or irradiat* or chemoradi* or radiochemo*)
- #8 #4 or #5 or #6 or 7
- #9 Any MeSH descriptor with qualifier(s): [Drug therapy - DT]
- #10 MeSH descriptor: [Antineoplastic Agents] explode all trees
- #11 MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] this term only
- #12 MeSH descriptor: [Chemotherapy, Adjuvant] explode all trees
- #13 chemo*
- #14 #9 or #10 or #11 or #12 or #13
- #15 #3 and #8 and #14

Appendix 2. MEDLINE search strategy

1. Uterine Cervical Neoplasms/
2. (cervi* adj5 (cancer* or neoplas* or carcinoma* or tumor* or tumour* or malignan*)).mp.
3. 1 or 2
4. radiotherapy.fs.
5. exp Radiotherapy/
6. exp Chemoradiotherapy/
7. (radiotherap* or radiat* or irradiat* or chemoradi* or radiochemo*).mp.
8. 4 or 5 or 6 or 7
9. drug therapy.fs.
10. exp Antineoplastic Agents/
11. Antineoplastic Combined Chemotherapy Protocols/

12. Chemotherapy, Adjuvant/
13. chemo*.mp.
14. 9 or 10 or 11 or 12 or 13
15. 3 and 8 and 14
16. randomized controlled trial.pt.
17. controlled clinical trial.pt.
18. randomized.ab.
19. placebo.ab.
20. clinical trials as topic.sh.
21. randomly.ab.
22. trial.ti.
23. 16 or 17 or 18 or 19 or 20 or 21 or 22
24. 15 and 23
25. exp animals/ not humans.sh.
26. 24 not 25

key: mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier, pt=publication type, ab=abstract, ti=title, sh=subject heading, fs=floating subheading, exp=exploded term

Appendix 3. EMBASE

1. exp uterine cervix tumor/
2. (cervi* adj5 (cancer* or neoplas* or carcinoma* or tumor* or tumour* or malignan*)).mp.
3. 1 or 2
4. rt.fs.
5. exp radiotherapy/
6. exp chemoradiotherapy/
7. (radiotherap* or radiat* or irradiat* or chemoradi* or radiochemo*).mp.
8. 4 or 5 or 6 or 7
9. dt.fs.
10. exp antineoplastic agent/
11. exp chemotherapy/
12. chemo*.mp.
13. 9 or 10 or 11 or 12
14. 3 and 8 and 13
15. crossover procedure/
16. double-blind procedure/
17. randomized controlled trial/
18. single-blind procedure/
19. random*.mp.
20. factorial*.mp.
21. (crossover* or cross over* or cross-over*).mp.
22. placebo*.mp.
23. (double* adj blind*).mp.
24. (singl* adj blind*).mp.
25. assign*.mp.
26. allocat*.mp.
27. volunteer*.mp.
28. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29. 14 and 28
30. (exp animal/ or nonhuman/ or exp animal experiment/) not human/
31. 29 not 30

key: [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

Appendix 4. The Cochrane Collaboration tool for assessing risk of bias in included studies

Random sequence generation

- Low risk of bias: e.g. participants assigned to treatments on basis of a computer-generated random sequence or a table of random numbers.
- High risk of bias: e.g. participants assigned to treatments on basis of date of birth, clinic ID number or surname or no attempt to randomly assign participants.
- Unclear risk of bias: e.g. not reported, information not available.

Allocation concealment

- Low risk of bias: e.g. where the allocation sequence could not be foretold.
- High risk of bias: e.g. allocation sequence could be foretold by participants, investigators or treatment providers.
- Unclear risk of bias: e.g. not reported.

Blinding of participants and personnel (not applicable)

Blinding of outcomes assessors

- Low risk of bias if outcome assessors were adequately blinded.
- High risk of bias if outcome assessors were not blinded to the intervention that the participant received.
- Unclear risk of bias if this was not reported or was unclear.

Incomplete outcome data

We recorded the proportions of participants whose outcomes were not reported at the end of the study. We coded a satisfactory level of loss to follow-up for each outcome as follows.

- Low risk of bias if less than 20% of participants were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms.
- High risk of bias if more than 20% of participants were lost to follow-up or reasons for loss to follow-up differed between treatment arms.
- Unclear risk of bias if loss to follow-up was not reported.

Selective reporting of outcomes

- Low risk of bias: e.g. review reports all outcomes specified in the protocol.
- High risk of bias: e.g. it is suspected that outcomes have been selectively reported.
- Unclear risk of bias: e.g. it is unclear whether outcomes had been selectively reported.

Other bias

- Low risk of bias if no source of bias is suspected and the trial appears to be methodologically sound.
- High risk of bias if the trial is suspected to have an additional bias.
- Unclear risk of bias if it is uncertain whether an additional bias may have been present.

Adopted from [Higgins 2011](#).

CONTRIBUTIONS OF AUTHORS

Siriwan Tangjitgamol and Kanyarat Katanyoo developed the review, searched for and determined the relevance of trials for the review, assessed their methodological quality, collected and extracted data and wrote the review. Pisake Lumbiganon supervised the drafts, provided methodological advice throughout the review, arbitrated over disagreements and advised over the content and presentation of the review. Sumonmal Manusirivithaya developed the protocol and reviewed the drafts and the final manuscript. Malinee Laopaiboon and Busaba Supawattanabodee developed the protocol and ensured scientific purity.

DECLARATIONS OF INTEREST

The review authors and their colleagues are conducting an RCT entitled 'Randomized controlled trial comparing concurrent chemoradiation versus concurrent chemoradiation followed by adjuvant chemotherapy in locally advanced cervical cancer patients.'

SOURCES OF SUPPORT

Internal sources

- Faculty of Medicine Vajira Hospital, University of Bangkok Metropolis, Thailand.
- Faculty of Medicine, Khon Kaen University, Thailand.
- Faculty of Public Health, Khon Kaen University, Thailand.

External sources

- Thailand Research Fund (Senior Research Scholar), Thailand.
- Thai Cochrane Network, Thailand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Failure after treatment, which was not stated in the protocol, was included in the review and meta-analysis. We determined that two main reasons justified the change. First, adjuvant chemotherapy is generally expected to have a systemic effect in controlling distant failure, and evidence from the meta-analysis should be useful for clinical practice. Second, data on this outcome were completely reported in both trials.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Combined Chemotherapy Protocols [*therapeutic use]; Chemoradiotherapy [*methods; mortality]; Chemotherapy, Adjuvant [adverse effects; methods; mortality]; Cisplatin [administration & dosage]; Deoxycytidine [administration & dosage; analogs & derivatives]; Fluorouracil [administration & dosage]; Mitomycin [administration & dosage]; Neoplasm Staging; Randomized Controlled Trials as Topic; Uterine Cervical Neoplasms [mortality; pathology; *therapy]

MeSH check words

Female; Humans



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Pneumococcal vaccination during pregnancy for preventing infant infection (Review)

Chaithongwongwatthana S, Yamasmit W, Limpongsanurak S, Lumbiganon P, Tolosa JE

Chaithongwongwatthana S, Yamasmit W, Limpongsanurak S, Lumbiganon P, Tolosa JE.

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	3
BACKGROUND	5
OBJECTIVES	6
METHODS	6
RESULTS	10
Figure 1.	11
DISCUSSION	13
AUTHORS' CONCLUSIONS	13
ACKNOWLEDGEMENTS	14
REFERENCES	14
CHARACTERISTICS OF STUDIES	17
DATA AND ANALYSES	26
Analysis 1.1. Comparison 1 Pneumococcal vaccine versus control vaccine, Outcome 1 Neonatal infection.	27
Analysis 1.2. Comparison 1 Pneumococcal vaccine versus control vaccine, Outcome 2 Pneumococcal colonization.	28
Analysis 1.5. Comparison 1 Pneumococcal vaccine versus control vaccine, Outcome 5 Percentage of mothers with seroprotection.	31
Analysis 1.6. Comparison 1 Pneumococcal vaccine versus control vaccine, Outcome 6 Adverse maternal effects.	32
APPENDICES	32
WHAT'S NEW	33
HISTORY	33
CONTRIBUTIONS OF AUTHORS	34
DECLARATIONS OF INTEREST	34
SOURCES OF SUPPORT	34
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	35
INDEX TERMS	35

Pneumococcal vaccination during pregnancy for preventing infant infection

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ABSTRACT

Background

Approximately 450,000 children worldwide die of pneumococcal infections each year. The development of bacterial resistance to antimicrobials adds to the difficulty of treatment of diseases and emphasizes the need for a preventive approach. Newborn vaccination schedules could substantially reduce the impact of pneumococcal disease in immunized children, but do not have an effect on the morbidity and mortality of infants less than three months of age. Pneumococcal vaccination during pregnancy may be a way of preventing pneumococcal disease during the first months of life before the pneumococcal vaccine administered to the infant starts to produce protection.

Objectives

To assess the effect of pneumococcal vaccination during pregnancy for preventing infant infection.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 July 2014) and reference lists of retrieved studies.

Selection criteria

Randomized controlled trials in pregnant women comparing pneumococcal vaccine with placebo or doing nothing, or with another vaccine to prevent infant infections.

Data collection and analysis

Two review authors independently assessed trials for inclusion and risk of bias, extracted data and checked them for accuracy. We contacted study authors for additional information.

Main results

Seven trials were included, but only six trials (919 participants) contributed data. There was no evidence that pneumococcal vaccination during pregnancy reduces the risk of neonatal infection (risk ratio (RR) 0.66; 95% confidence interval (CI) 0.30 to 1.46; two trials, 241 pregnancies, *low quality evidence*). Although the data suggest an effect in reducing pneumococcal colonization in infants by 16 months of age (average RR 0.33; 95% CI 0.11 to 0.98; one trial, 56 pregnancies), there was no evidence of this effect in infants at two to three months of age (average RR 1.13; 95% CI 0.46 to 2.78; two trials, 146 pregnancies, *low quality evidence*) or by six to seven months of age (average RR 0.67, 95% CI 0.22 to 2.08; two trials, 148 pregnancies, *low quality evidence*). None of the trials included in this review reported neonatal death as a result of pneumococcal infection.

Neonatal antibody levels were reported as geometric mean and 95% CI. There were inconsistent results between studies. Two studies showed significantly higher immunoglobulin G (IgG) levels in cord blood in the pneumococcal vaccine group when compared with the control group for all serotypes. In contrast, another trial showed no difference in neonatal antibody levels between the pneumococcal vaccine group and the control group.

Maternal antibody levels were also reported as geometric mean and 95% CI. One study showed significantly higher IgG levels in maternal serum in women immunized with pneumococcal vaccine when compared with control vaccine regardless of any serotypes. Another study showed significantly higher maternal antibody levels only for serotype 14, but no evidence of an effect for other serotypes.

The percentage of women with seroprotection was measured in one trial at delivery and at 12 months post-delivery. At delivery, results favored the intervention group for serotype 6 (RR 1.49, 95% CI 1.31 to 1.69), serotype 14 (RR 1.40, 95% CI 1.25 to 1.56) and serotype 19 (RR 2.29, 95% CI 1.89 to 2.76). There were no group differences seen at 12 months post-delivery for serotypes 6 or 14 (RR 1.06, 95% CI 1.00 to 1.12 and RR 1.06, 95% CI 0.98 to 1.15, respectively), but results favored the intervention group for serotype 19 (RR 1.59, 95% CI 1.37 to 1.85).

No significant difference for tenderness at the injection site between women who received pneumococcal vaccine and those who received control vaccine (average RR 3.20; 95% CI 0.32 to 31.54; two trials, 130 women).

The overall quality of evidence is low for primary outcomes. Most outcomes had wide confidence intervals crossing the line of no effect, and most of the included trials had small numbers of participants and few events which led to downgrading evidence for imprecision of findings.

Authors' conclusions

There is insufficient evidence to assess whether pneumococcal vaccination during pregnancy could reduce infant infections.

PLAIN LANGUAGE SUMMARY

Pneumococcal vaccination during pregnancy for preventing infant infection

There is not enough evidence to assess whether using pneumococcal vaccination during pregnancy can prevent infant infections.

Although the incidence of invasive pneumococcal disease is variable across the world, the rate of serious illness or death is high in children who get this infection. The *Streptococcus pneumoniae* (pneumococcus) organism colonizes the upper respiratory tract and can cause bacteremia, meningitis, pneumonia and other lower respiratory tract, and upper respiratory tract infections, including otitis media and sinusitis. Newborn vaccination schedules of three primary doses with a booster dose could reduce the impact of pneumococcal disease in immunized children, but these vaccinations have no protective effect in infants less than three months of age. Maternal pneumococcal immunization during pregnancy may be a way of preventing pneumococcal disease during the infant's first months of life. We included seven randomized controlled trials. A total of 919 pregnant women participated in the six randomized controlled trials that contributed data to this review. The trials compared 23-valent pneumococcal polysaccharide vaccine with control vaccine. All women received a single injection of pneumococcal or control vaccine (where used). The women's mean gestational age at the time of immunization was between 27 and 38 weeks, where stated. Only two trials with 241 pregnancies reported on neonatal infections. This was not enough information to say whether pneumococcal vaccination during pregnancy led to fewer infant infections. Two trials with 146 pregnancies reported on infant nasal carriage of pneumococci (pneumococcal colonization), which was not enough evidence to show an effect in reducing colonization at two to three months of age or six to seven months of age. The included trials were of reasonable quality. There was no difference between pneumococcal vaccine and control vaccine for tenderness at the injection site. No serious adverse events were reported in the trials.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Pneumococcal vaccine versus control vaccine for preventing infant infection						
Patient or population: Pregnant women undergoing vaccination to prevent infant infection Settings: Studies were located in Bangladesh, Brazil, The Gambia and the USA. Intervention: Pneumococcal vaccine versus control vaccine						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Pneumococcal vaccine versus control vaccine				
Neonatal death due to pneumococcal infection			0	0	Not estimable	None of the included studies in this review measured the primary outcome of neonatal death due to pneumo- coccal infection
Neonatal infection - Pneumonia Follow-up: 1 year	Study population		RR 0.58 (0.18 to 1.9)	149 (1 study)	⊕⊕○○ low ¹	
	93 per 1000	54 per 1000 (17 to 177)				
Neonatal infection - Meningitis Follow-up: 1 year	Study population		RR 3.04 (0.13 to 73.44)	149 (1 study)	⊕⊕○○ low ¹	
	0 per 1000	0 per 1000 (0 to 0)				
Neonatal infection - Otitis media Follow-up: 1 year	Study population		RR 0.14 (0.01 to 2.75)	149 (1 study)	⊕⊕○○ low ¹	

	40 per 1000	6 per 1000 (0 to 110)			
Neonatal infection - All infections	Study population		RR 0.66 (0.3 to 1.46)	241 (2 studies)	⊕⊕○○ low ¹
Follow-up: 3-12 months	115 per 1000	76 per 1000 (34 to 168)			
Pneumococcal colonization - At 2-3 months of age	Study population		RR 1.13 (0.46 to 2.78)	146 (2 studies)	⊕⊕○○ low ¹
Follow-up: 2-3 months	133 per 1000	150 per 1000 (61 to 368)			
Pneumococcal colonization - By 6-7 months of age	Study population		RR 0.67 (0.22 to 2.08)	148 (2 studies)	⊕⊕○○ low ¹
Follow-up: 6-7 months	271 per 1000	181 per 1000 (60 to 563)			

*The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Wide confidence interval crossing the line of no effect, few events and small sample size (-2).

BACKGROUND

Description of the condition

Infections caused by *Streptococcus pneumoniae* (pneumococcus) are a major cause of morbidity and mortality throughout the world (WHO 2012). Pneumococcus is a leading cause of illness in young children and causes illness and death among the elderly and persons who have certain underlying medical conditions. The organism colonizes the upper respiratory tract and can cause the following types of illnesses: (a) invasive pneumococcal infections, including bacteremia and meningitis; (b) pneumonia and other lower respiratory tract infections; and (c) upper respiratory tract infections, including otitis media and sinusitis. Invasive pneumococcal diseases are less common than non-invasive manifestations, but cause high mortality. Each year, approximately 330,000 to 529,000 children worldwide, mostly in low- to middle-income countries, die of pneumococcal infections (WHO 2012). The development of resistance to antimicrobials by the bacteria adds to the difficulty of treatment of diseases and emphasizes the need for a preventive approach.

Regional differences in incidence of invasive pneumococcal disease have been noted. A 10-year surveillance in the Oxfordshire region of England, found that the annual incidence of invasive pneumococcal disease among children under five years of age prior to implementation of the pneumococcal vaccine was 24.3 per 100,000 persons (95% confidence interval 21.0 to 27.7) (Foster 2008). A population-based study carried out in a rural area of Bangladesh estimated the incidence of invasive pneumococcal disease among children to be 86 cases per 100,000 person-years (Arifeen 2009). In the United States, the routine use of pneumococcal vaccine beginning in 2000 has had a substantial impact on the epidemiology of pneumococcal disease in children. In infants younger than five years, rates of invasive pneumococcal disease have decreased from 98.7 cases per 100,000 population during 1998 and 1999 to 23.6 cases per 100,000 population in 2007 (Pilishvili 2010). Similar findings were reported in European countries. After widespread pneumococcal vaccination, there was a mean decline in the incidence of invasive pneumococcal disease in children aged less than two years from 32.5 to 23.4/100,000 (Isaacman 2010).

Description of the intervention

There are two types of pneumococcal vaccine available, polysaccharide vaccines and polysaccharide/protein conjugate vaccines. The 23-valent polysaccharide vaccine (PPV23) contains polysaccharide antigen from 23 types of pneumococcal bacteria (serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F), which cause 85% to 90% of bacteremic pneumococcal disease in adults. More than 80% of healthy adults who receive PPV23 develop antibodies against the

serotypes contained in the vaccine within two to three weeks after vaccination; however, the vaccine is relatively poor at producing immunity in children less than two years old (Klouwenberg 2008). The pneumococcal conjugated vaccine (PCV) is much better at producing immunity in infants than pure polysaccharide vaccines (Black 2000; Klouwenberg 2008). In 2000, the 7-valent pneumococcal conjugated vaccine (PCV7) was recommended in the United States for immunization of infants (CDC 2000). PCV-7 includes the seven most frequent polysaccharides (serotypes 4, 6B, 9V, 14, 18C, 19F, 23F) in pneumococcal infections of the young child. Newborn vaccination schedules consist of three primary doses routinely plus a booster dose. After four doses, more than 90% of healthy infants develop antibodies to all seven serotypes contained in the vaccine. In a large trial, PCV7 was shown to reduce invasive disease caused by vaccine serotypes by 97%; however, it was less effective against acute otitis media (Black 2000). Local reactions following PCV7 occur in 10% to 20% of recipients and are more common with the fourth dose than the first three doses. No severe adverse events attributable to PCV7 have been reported. The vaccine could substantially reduce the impact of pneumococcal disease in immunized children (Isaacman 2010; Pilishvili 2010); however, it does not have an effect on the morbidity and mortality of the younger infants, especially those less than three months of age. This may be due to the fact that serum IgG (immunoglobulin G) antibodies against polysaccharides increase only after the second and third vaccine doses are administered (Rennels 1998).

PCV7 given to the children has had a substantial effect on pneumococcal disease in the United States since its introduction in 2000. A large, population-based surveillance system monitoring invasive pneumococcal disease in a population of nearly 20 million persons in the United States, found that rates of invasive pneumococcal disease in children younger than two years of age were 68.6% lower in 2001 compared with rates of disease before the vaccine was introduced (Whitney 2003). Furthermore, widespread vaccination of children with PCV7 has shown a 'herd effect' in decreasing the carriage rate of *S. pneumoniae* in children, who are an important vector of *S. pneumoniae* to other children and adults (Dagan 2000; Pilishvili 2010). Data from the same surveillance indicate that unvaccinated adults are benefiting from the vaccination of children. Infection rates in adults fell 8% to 32% when compared with the average rates in 1998 and 1999 (Whitney 2003). However, invasive pneumococcal disease caused by non-PCV7 serotypes has increased and partially offset the reductions (CDC 2010; Pilishvili 2010). Overall, rates of invasive pneumococcal disease have remained stable at 22 to 25 cases per 100,000 since 2002 (CDC 2010; Pilishvili 2010). An increase in disease due to non-PCV-7 serotypes and the need for broader serotype coverage to address the global disease burden provides a rationale for a second-generation conjugate vaccine, 10-valent pneumococcal conjugated vaccine (PCV10, including serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) and 13-valent pneumococcal conjugated vaccine (PCV13,

including serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) (Grijalva 2011; WHO 2012). The Advisory Committee on Immunization Practices in the United States has recommended the use of PCV13 for immunization of infants since 2010 (CDC 2010) and the World Health Organization has recommended to replace PCV7 by PCV10 or PCV13 for immunization of infants in 2012 (WHO 2012).

How the intervention might work

Maternal immunization could help to prevent the two to three million neonatal and early infant deaths that occur in low- to middle-income countries each year (Greenwood 2003). Maternal pneumococcal immunization may be a way of preventing pneumococcal disease during the first months of life before infant-administered pneumococcal conjugate vaccine starts to produce protection. This strategy has the potential to impact on public health, as has been seen by the prevention of tetanus neonatorum through maternal immunization (Khan 2013). An effective delivery system for maternal immunization already exists and, because of the success of maternal tetanus immunization, this approach to the prevention of serious illness or death in young infants is widely accepted by the general population.

Why it is important to do this review

There are clinical studies on maternal pneumococcal immunization to prevent infant infection, but information regarding effectiveness of the intervention is not known.

OBJECTIVES

To assess the effectiveness of pneumococcal vaccine administered to pregnant women in preventing pneumococcal infection in the infant.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials. Quasi-randomized controlled trials were not included.

Types of participants

Healthy women with uncomplicated pregnancies.

Types of interventions

Pneumococcal vaccine (polysaccharide or conjugate) compared with placebo or doing nothing, or with another vaccine.

Types of outcome measures

Primary outcomes

(1) Neonatal pneumococcal infection:

- pneumonia (diagnosed by clinical findings and radiological or laboratory findings);
- meningitis (diagnosed by clinical findings and laboratory findings);
- bacteremia/sepsis (diagnosed by clinical findings and laboratory findings);
- neonatal death (due to pneumococcal infection);
- otitis media (diagnosed by clinical findings and laboratory findings).

(2) Neonatal pneumococcal colonization:

- at two to three months of age;
- by six to seven months of age.

Secondary outcomes

- (1) Neonatal antibody levels.
- (2) Adverse neonatal effects.
- (3) Maternal antibody levels.
- (4) Incidence of maternal pneumococcal colonization during labor.
- (5) Adverse maternal effects.
- (6) Neonatal pneumococcal colonization by 16 months of age.

Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (31 July 2014).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);

2. weekly searches of MEDLINE;
3. weekly searches of Embase;
4. handsearches of 30 journals and the proceedings of major conferences;

5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We did not apply any language restrictions.

(Please see [Appendix 1](#) for details of additional searches carried out in the initial version of the review ([Chaithongwongwatthana 2006](#)).)

Searching other resources

We searched cited references from retrieved articles for additional studies. We reviewed abstracts and letters to the editor to identify randomized controlled trials that have not been published. If we identified a randomized controlled trial, we contacted the primary investigator directly to obtain further data. We reviewed editorials, indicating expert opinion, to identify and ensure that no key studies were missed for inclusion in this review.

We did not apply any language restrictions.

Data collection and analysis

For methods used in the previous version of this review, see [Chaithongwongwatthana 2012](#).

For this update, the following methods were used for assessing the two reports that were identified as a result of the updated search. The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted the third review author.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted the

third review author. Data were entered into Review Manager software ([RevMan 2014](#)) and checked for accuracy.

When information regarding any of the above was unclear, we contacted authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). Any disagreement was resolved by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we planned to re-include missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomization);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we had about other possible sources of bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we planned to assess the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. In future updates, we will explore the impact of the level of bias through undertaking sensitivity analyses - see [Sensitivity analysis](#).

For this update, the quality of the evidence was assessed using the GRADE approach (Schunemann 2009) in order to assess the quality of the body of evidence relating to the following outcomes for the main comparisons.

1. Neonatal infection - pneumonia
2. Neonatal infection - meningitis
3. Neonatal infection - otitis media
4. Neonatal infection - all
5. Neonatal infection - neonatal death
6. Pneumococcal colonization - two to three months
7. Pneumococcal colonization - six to seven months

GRADE profiler (GRADE 2008) was used to import data from Review Manager 5.3 (RevMan 2014) in order to create a 'Summary of findings' table. A summary of the intervention effect and a measure of quality for each of the above outcomes was produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

The primary outcomes were included in the [Summary of findings for the main comparison](#). For neonatal infection, none of the included trials in this review reported the outcome of neonatal death. Neonatal pneumococcal colonization by 16 months of age was reported in one trial, but it was not included as a primary outcome or in the 'Summary of findings' table because the colonization at this time point may be confounded by neonatal vaccination.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

We did not identify any continuous outcomes. We planned to use the mean difference if outcomes were measured in the same way between trials. We would have used the standardized mean difference to combine trials that measured the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomized trials

For this update we did not include any cluster-randomized trials in the review. If in future updates eligible cluster-randomized trials are identified, we will include these cluster-randomized trials in the analyses along with individually-randomized trials. We will adjust their sample sizes or standard errors using the methods described in the *Handbook* using an estimate of the intra-cluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomized trials and individually-randomized trials, we plan to synthesize the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomization unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomization unit and perform a sensitivity analysis to investigate the effects of the randomization unit.

Dealing with missing data

For included studies, we noted levels of attrition. In future updates, if more eligible studies are included, the impact of including studies with high levels of missing data in the overall assessment of treatment effect will be explored by using sensitivity analysis. For all outcomes, analyses were carried out, as far as possible, on an intention-to-treat basis i.e. we attempted to include all participants randomized to each group in the analyses. The denominator for each outcome in each trial was the number randomized minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the τ^2 , I^2 and χ^2 statistics. We regarded heterogeneity as substantial if an I^2 was greater than 30% and either the τ^2 was greater than zero, or there was a low P value (less than 0.10) in the χ^2 test for heterogeneity. Had we identified substantial heterogeneity (above 30%), we planned to explore it by pre-specified subgroup analysis.

Assessment of reporting biases

In future updates, if there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar.

Where there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average range of possible treatment effects and discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we did not combine trials. Where we used random-effects analyses, the results were presented as the average treatment effect with 95% confidence intervals, and the estimates of τ^2 and I^2 .

Subgroup analysis and investigation of heterogeneity

Had we identified substantial heterogeneity, we planned to investigate it using subgroup analyses and sensitivity analyses. We would have considered whether an overall summary was meaningful, and if it was, we planned to use random-effects analysis to produce it. We planned to carry out the following subgroup analyses:

1. types of pneumococcal vaccine (polysaccharide versus conjugate);
2. countries of participants (high-income versus low- to middle-income).

The following outcomes were planned for use in subgroup analyses:

1. neonatal pneumococcal infection;
2. neonatal pneumococcal colonization.

There were too few trials included in this review to conduct meaningful subgroup analysis.

We assessed subgroup differences by interaction tests available within RevMan (RevMan 2014). We reported the results of subgroup analyses quoting the χ^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We planned to carry out sensitivity analyses to explore the effect of trial quality assessed by concealment of allocation, high attrition rates, or both, with poor quality studies being excluded from the analyses in order to assess whether this makes any difference to the overall result.

There were too few trials included in this review to conduct meaningful sensitivity analysis.

RESULTS

Description of studies

Results of the search

We identified 10 studies as potentially eligible for inclusion in this review. We included seven trials and excluded two trials, one trial is ongoing (Dunbar 2007). Seven new reports were identified in the updated search. All of them reported new information from the two included trials (Lopes 2009; Zaman 2008).

Included studies

One trial (Obaro 2004) did not contribute data toward the analyses because it did not report the outcomes of interest. A total of 919 pregnant women participated in the other six included studies comparing 23-valent pneumococcal polysaccharide vaccine with control vaccine (O' Dempsey 1996; Munoz 2001; Shahid 1995; Zaman 2008) or no vaccine (Lopes 2009; Quiambao 2003). The O' Dempsey 1996 trial included 75 women in each group. The Munoz 2001 trial used a 2:1 randomization scheme with 20 women in the vaccine group and 40 women in control group. The Shahid 1995 trial included 36 women in vaccine group and 34 women in control group. The Zaman 2008 trial included 168 women in vaccine group and 172 women in control group. Lopes 2009 was a trial with three arms. We have included data from two of the arms: 47 women in a control group (no vaccine) and 45 women who received vaccine at 30 to 34 weeks of gestation. The third arm involved 47 women who received vaccine after delivery; these data were not included from our analyses. Quiambao 2003 employed a 2:1 randomization scheme and included 106 women in vaccine group and 54 women in control group.

Participants

This review includes data from six trials with a total of 919 pregnant women. A total of 497 women were randomized to be immunized with pneumococcal polysaccharide vaccine and 422 women were randomized to control vaccines. The included trials were conducted in various settings; one in Brazil (Lopes 2009), one in the United States (Munoz 2001), two in the Gambia (O' Dempsey 1996; Obaro 2004), one in the Philippines (Quiambao 2003), and two in Bangladesh (Shahid 1995; Zaman 2008). All participants were healthy women with an uncomplicated pregnancy. Lopes 2009 and Obaro 2004 had no available data on participants' mean age but for the other included trials (Munoz 2001; O' Dempsey

1996; Quiambao 2003; Shahid 1995; Zaman 2008), the mean age of the women in each study was 30.2 (Munoz 2001), 22.0 (O' Dempsey 1996), 26.8 (Quiambao 2003), 25.6 (Shahid 1995), and 24.9 (Zaman 2008) years.

Interventions

All trials used a 23-valent pneumococcal polysaccharide vaccine compared with control vaccine or no vaccine. One trial (Munoz 2001) used *Hemophilus influenzae* conjugate vaccine as the control; two trials (O' Dempsey 1996; Shahid 1995) used meningococcal vaccine as the control; one trial (Zaman 2008) used inactivated influenza vaccine as the control while the other two trials (Lopes 2009; Quiambao 2003) had no control vaccine. All women received a single injection of pneumococcal or control vaccine (where used). The mean gestational age at the time of immunization in each study was no available data (Lopes 2009), 33.3 (Munoz 2001), 38.0 (O' Dempsey 1996), 27.3 weeks (Quiambao 2003), 32.3 (Shahid 1995), and no available data (Zaman 2008). The mean interval between immunization and delivery in each study was 43.6 (Munoz 2001), 44.1 (O' Dempsey 1996), 51.4 (Shahid 1995), 54.9 (Zaman 2008), not available data (Lopes 2009) and 76.3 days (Quiambao 2003) respectively.

Outcomes

Two studies reported the incidence of neonatal infection (Lopes 2009; O' Dempsey 1996). Two trials reported the incidence of neonatal pneumococcal colonization (Lopes 2009; Munoz 2001). Three trials (Munoz 2001; O' Dempsey 1996; Quiambao 2003) reported neonatal antibody levels as geometric mean with 95% confidence interval. Three trials (Munoz 2001; O' Dempsey 1996; Shahid 1995) reported maternal antibody levels. One trial reported (Zaman 2008) the percentage of mothers with seroprotection. No serious adverse reactions attributable to the vaccines were observed in all studies (see Characteristics of included studies).

Excluded studies

We excluded two trials (Daly 2003; Glezen 2000). See Characteristics of excluded studies table.

Risk of bias in included studies

One trial was at low risk of bias (Zaman 2008). All the remaining trials were at unclear risk of selection bias. High risk for attrition bias was noted in the two trials (Quiambao 2003; Shahid 1995). The risk of bias in the included trials is summarized in the 'Risk of bias' graph (Figure 1).

Figure 1. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Lopes 2009	?	?	+	+	+	+	+
Munoz 2001	?	?	+	+	+	+	+
O'Dempsey 1996	?	?	+	+	+	+	?
Obaro 2004	+	?	+	+	+	+	+
Quiambao 2003	?	?	+	+	-	+	+
Shahid 1995	?	?	+	+	-	+	+
Zaman 2008	+	+	+	+	+	+	+

Allocation

Only one trial ([Zaman 2008](#)) described the method of random allocation and allocation concealment. The other six trials had an unclear risk of selection bias.

Blinding

Four trials ([Munoz 2001](#); [O' Dempsey 1996](#); [Shahid 1995](#); [Zaman 2008](#)) were double-blind studies. Although the other two trials were not double-blind studies, the risk of detection bias was low because the reported outcomes were objective outcomes.

Incomplete outcome data

Only one trial ([Lopes 2009](#)) had complete follow-up. There were two trials ([Quiambao 2003](#); [Shahid 1995](#)) that had high risk for attrition bias due to high proportion of incomplete outcome data.

Selective reporting

All trials had low risk for reporting bias.

Other potential sources of bias

None.

Effects of interventions

See: [Summary of findings for the main comparison](#)
Pneumococcal vaccine versus control vaccine for preventing infant infection

Comparison

Primary outcomes

Neonatal infections

Only two trials ([Lopes 2009](#); [O' Dempsey 1996](#)) with 241 pregnancies reported these outcomes. There was insufficient evidence to show an effect of maternal pneumococcal vaccine during pregnancy in reduction of neonatal infections (risk ratio (RR) 0.66; 95% confidence interval (CI) 0.30 to 1.46) including pneumonia (RR 0.58; 95% CI 0.18 to 1.90), meningitis (RR 3.04; 95% CI 0.13 to 73.44), and otitis media (RR 0.14; 95% CI 0.01 to 2.75). See [Analysis 1.1](#).

None of the included trials in this review reported the outcome of neonatal death due to pneumococcal infection.

Neonatal pneumococcal colonization

Two studies ([Lopes 2009](#); [Munoz 2001](#)) with 148 pregnancies reported this outcome at several time points and according to three serotypes (6, 14 and 19). There was not enough evidence to show an effect of maternal pneumococcal vaccination in reduction of neonatal nasal carriage of pneumococci at two to three months of age (average RR 1.13; 95% CI 0.46 to 2.78) or by six to seven months of age (average RR 0.67; 95% CI 0.22 to 2.08, $I^2 = 54\%$, $\text{Tau}^2 = 0.38$). Nevertheless, the results showed a statistically significant decrease in the incidence of pneumococcal colonization in infants by 16 months of age (RR 0.33; 95% CI 0.11 to 0.98; one study, 56 infants). See [Analysis 1.2](#). One study with 92 women ([Lopes 2009](#)) found no group differences in pneumococcal colonization according to serotype 6, 14 or 19 (RR 0.12, 95% CI 0.01 to 2.09; not estimable; and RR 2.09, 95% CI 0.40 to 10.85, respectively).

Heterogeneity was noted for neonatal colonization at the time point six to seven months of age. This substantial heterogeneity may be from participants from different settings. [Lopes 2009](#) conducted the trial in Brazil while [Munoz 2001](#) conducted the trial in the United States. However, no statistical significant difference between the vaccine group and control group was found in either trial (RR 1.04; 95% CI 0.48 to 2.27 in [Lopes 2009](#) and RR 0.32; 95% CI 0.08 to 1.29 in [Munoz 2001](#)).

Secondary outcomes

Neonatal antibody levels

Antibody levels were reported as geometric means and 95% CIs. There were inconsistent results between studies. Two studies ([Munoz 2001](#); [Quiambao 2003](#)) showed significantly higher immunoglobulin G (IgG) levels in cord blood in the pneumococcal vaccine group when compared with the control group for all serotypes. In contrast, [O' Dempsey 1996](#) showed no difference in neonatal antibody levels between the pneumococcal vaccine group and the control group. See [Analysis 1.3](#).

Maternal antibody levels

Antibody levels were reported as geometric means and 95% CIs. One study ([Munoz 2001](#)) showed significantly higher IgG levels in maternal serum in women immunized with pneumococcal vaccine when compared with control vaccine regardless of any serotypes. The other study ([O' Dempsey 1996](#)) showed significantly higher maternal antibody levels only for serotype 14, but no evidence of an effect of the pneumococcal vaccine resulting in an increase in maternal antibody levels in the other serotypes. See [Analysis 1.4](#).

Percentage of mothers with seroprotection was also reported in one trial with 340 women (Zaman 2008). This outcome was measured according to serotype (6, 14 or 19) and at two time points (delivery and 12 months post-delivery). Results favored the intervention group for serotype 6 at delivery (RR 1.49, 95% CI 1.31 to 1.69); serotype 14 at delivery (RR 1.40, 95% CI 1.25 to 1.56) and serotype 19 at delivery (RR 2.29, 95% CI 1.89 to 2.76). There were no group differences seen at 12 months post-delivery for serotypes 6 or 14 (RR 1.06, 95% CI 1.00 to 1.12 and RR 1.06, 95% CI 0.98 to 1.15, respectively). Results favored the intervention group for serotype 19 measured at 12 months post delivery (RR 1.59, 95% CI 1.37 to 1.85). See Analysis 1.5.

Adverse maternal effects

Two studies (Munoz 2001; Shahid 1995) reported tenderness at the injection site but this was not significantly different between the intervention and control groups (average RR 3.20; 95% CI 0.32 to 31.54, $I^2 = 79\%$, $\text{Tau}^2 = 2.24$ (Analysis 1.6)). The substantial heterogeneity may be from the different control vaccine used in the trials. Munoz 2001 used *Hemophilus influenzae* type b conjugate vaccine as control and found significant higher rate of tenderness in the pneumococcal vaccine group (RR 12.00; 95% CI 1.55 to 93.01). Shahid 1995 used meningococcal vaccine as control and found no significant difference of tenderness between the groups (RR 1.28; 95% CI 0.77 to 2.13).

DISCUSSION

Summary of main results

There was no evidence of an effect of pneumococcal vaccination during pregnancy in preventing neonatal infections; however, there were only two trials (Lopes 2009; O' Dempsey 1996) reporting this outcome. The power to detect this effect might be too low because of a small sample size. Results of one study (Munoz 2001) suggested that maternal pneumococcal vaccination can reduce the risk of pneumococcal colonization by 16 months of age, but no effect was shown at earlier ages.

An inconsistent result between two trials (Munoz 2001; Shahid 1995) was shown regarding tenderness at the injection site. This may be due to the different control vaccines used in the studies. Although there tends to be increased tenderness among women injected with pneumococcal vaccine, this symptom lasted only a few days after injection and no serious adverse events were reported in all of the trials.

Overall completeness and applicability of evidence

There are some limitations that should be considered when interpreting the results of this review. First, neonatal infection, the most significant outcome, was only reported in two trials with small numbers of participants. Neonatal death due to pneumococcal infections was not reported in any included trial. Second, the effect on neonatal pneumococcal colonization at 16 months of age with no effect demonstrated at two to seven months may not be due to the vaccine administered during pregnancy. There was no detail regarding the confounding factors or co-intervention reported in the trial. The included studies did not report on breastfeeding or antibody level in breast milk that may impact on antibody transfer to the neonates.

Quality of the evidence

Only one trial (Zaman 2008) described the precise method of random allocation and demonstrated method of allocation concealment. Four trials (Munoz 2001; O' Dempsey 1996; Shahid 1995; Zaman 2008) were double-blind studies. Only one trial (Lopes 2009) had complete follow-up.

Overall, the quality of evidence is low for all outcomes (Summary of findings for the main comparison). Outcomes had wide confidence intervals crossing the line of no effect, and included trials had small numbers of participants and few events, which led to downgrading evidence for imprecision of findings. There were no included studies that reported the primary outcome of neonatal death due to pneumococcal infection, but this important outcome is included in the GRADE table to highlight this gap in the evidence.

Potential biases in the review process

None.

Agreements and disagreements with other studies or reviews

A non-randomized study in Papua New Guinea (Lehmann 2002) compared neonatal antibody level between women who were immunized with 23-valent pneumococcal polysaccharide vaccine at 28 to 38 weeks' gestation and unimmunized women. The results were similar to the two included studies (Munoz 2001; Quiambao 2003). Geometric mean antibody titers were significantly higher in children of the immunized mothers than in those of the unimmunized group.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence from randomized controlled trials to support the use of pneumococcal vaccination during pregnancy for preventing infant infections. Pneumococcal vaccine is recommended for administration to pregnant women when they have underlying medical conditions for preventing maternal infections (ACOG 2003). None of the studies reported risk from the vaccine to fetus. Risk to a developing fetus from vaccination of the mother during pregnancy is primarily theoretical. No evidence exists of risk from vaccinating pregnant women with inactivated virus or bacterial vaccines or toxoids (CDC 2011). The benefits of vaccinating pregnant women usually outweigh potential risks when the likelihood of disease exposure is high, when infection would pose a risk to the mother or fetus, and when the vaccine is unlikely to cause harm.

One of the strategies to prevent infection in the neonatal and early infant period is neonatal vaccination. Two recent trials (Pomat 2013; Scott 2011) showed impressive results of earlier PCV7 administration to the newborn (at birth or shortly after birth). Although no clinical outcomes have yet been reported, both trials demonstrated that neonatal PCV7 vaccination was safe, immunogenic and not associated with immune tolerance. Vaccination beginning at birth may be a considerable option to minimize invasive pneumococcal disease in these young infants.

Implications for research

The review included a small number of randomized controlled

trials on pneumococcal vaccination during pregnancy, therefore, they may not have enough power to detect the effectiveness on preventing infant infections. Future trials need to choose the vaccine type as well as the timing of vaccination that could maximize maternal immunogenicity and antibody transfer to the fetus. A new approach using recombinant pneumococcal surface protein A (PspA) as a protein-based vaccine has been investigated in mice (Kono 2011).

None of the included studies in this review reported the primary outcome of neonatal death due to pneumococcal infection.

As previously discussed, the future vaccine formulations containing additional serotypes and earlier administration to the newborn needs to be evaluated for its effectiveness in reducing invasive pneumococcal disease in children. If it is the case, trials of pneumococcal vaccination during pregnancy for preventing infant infection may not be needed.

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Whitney CG, Farley MM, Hadler J, Harrison LH, Bennett NM, Lynfield R, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *New England Journal of Medicine* 2003; **348**:1737–46.

WHO 2012

World Health Organization. Pneumococcal vaccines WHO position paper - 2012. *Weekly Epidemiological Record* 2012; **87**(14):129–144. [PUBMED: 24340399]

References to other published versions of this review**Chaithongwongwatthana 2004**

Chaithongwongwatthana S, Yamasmit W, Limpongsanurak S, Lumbiganon P, DeSimone JA, Baxter JK, et al. Pneumococcal vaccination during pregnancy for preventing

infant infection. *Cochrane Database of Systematic Reviews* 2004, Issue 3. [DOI: 10.1002/14651858.CD004903]

Chaithongwongwatthana 2006

Chaithongwongwatthana S, Yamasmit W, Limpongsanurak S, Lumbiganon P, DeSimone JA, Baxter JK, et al. Pneumococcal vaccination during pregnancy for preventing infant infection. *Cochrane Database of Systematic Reviews* 2006, Issue 1. [DOI: 10.1002/14651858.CD004903.pub2]

Chaithongwongwatthana 2012

Chaithongwongwatthana S, Yamasmit W, Limpongsanurak S, Lumbiganon P, DeSimone JA, Baxter JK, et al. Pneumococcal vaccination during pregnancy for preventing infant infection. *Cochrane Database of Systematic Reviews* 2012, Issue 7. [DOI: 10.1002/14651858.CD004903.pub3]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Lopes 2009

Methods	Pregnant women were randomly assigned to one of three groups for the study	
Participants	Country: Brazil. Number: 47 women in the control group (no vaccine); 45 women received vaccine at 30-34 weeks of gestation; and 47 women received vaccine after delivery Mean age: data not available. Mean gestational age: data not available.	
Interventions	23-valent pneumococcal polysaccharide vaccine.	
Outcomes	Incidence of neonatal infection. Incidence of infant pneumococcal colonization. Maternal antibody levels (GM).	
Notes	Data from women received vaccine after delivery were excluded from analysis	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details were not reported.
Allocation concealment (selection bias)	Unclear risk	Details were not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lack of blinding would be unlikely to affect results.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Lack of blinding would be unlikely to affect results.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All infants completed follow-up at 3 months old.
Selective reporting (reporting bias)	Low risk	All outcomes were predefined and reported.
Other bias	Low risk	The trial appears to be free of industry sponsorship.

Munoz 2001

Methods	The study was a prospective, double-blind, randomized, controlled trial	
Participants	Country: United States. Number: 20 women in the intervention group and 40 women in the control group Mean age: 30.2 years. Mean gestational age: 33.3 weeks.	
Interventions	23-valent pneumococcal polysaccharide vaccine vs <i>Hemophilus influenzae</i> type b conjugate vaccine.	
Outcomes	Incidence of neonatal and infant pneumococcal colonization. Neonatal antibody levels (GM). Maternal antibody levels (GM). Incidence of tenderness at the injection site.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details were not reported.
Allocation concealment (selection bias)	Unclear risk	Details were not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind".
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/60 were lost to follow-up.
Selective reporting (reporting bias)	Low risk	All outcomes were predefined and reported.
Other bias	Low risk	The trial appears to be free of industry sponsorship.

O' Dempsey 1996

Methods	Women were randomized to receive either pneumococcal vaccine or control vaccine	
Participants	Country: The Gambia. Number: 75 women in the intervention group and 75 women in the control group Mean age: 22.0 years. Mean gestational age: 38.0 weeks.	
Interventions	23-valent pneumococcal polysaccharide vaccine vs meningococcal vaccine	
Outcomes	Incidence of neonatal pneumonia. Incidence of neonatal meningitis. Incidence of neonatal otitis media. Neonatal antibody levels (GM). Maternal antibody levels (GM).	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details were not reported.
Allocation concealment (selection bias)	Unclear risk	Details were not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lack of blinding would be unlikely to affect results.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Lack of blinding would be unlikely to affect results.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1/150 were lost to follow-up.
Selective reporting (reporting bias)	Low risk	All outcomes were predefined and reported.
Other bias	Unclear risk	Vaccines were provided by industry sponsorship, but none of the authors affiliated with the company

Obaro 2004

Methods	The study was a randomized, double-blind, controlled trial.	
Participants	Country: The Gambia. Number: 56 women in the intervention group and 57 women in the control group Mean age: data not available. Mean gestational age: data not available.	
Interventions	23-valent pneumococcal polysaccharide vaccine vs meningococcal vaccine	
Outcomes	Pneumococcal polysaccharide-specific s-IgA antibody concentrations in breast milk	
Notes	Did not contribute data to analysis.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were vaccinated with 1 dose of either a pneumococcal vaccine or control by computer-generated random assignment
Allocation concealment (selection bias)	Unclear risk	Details were not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two mothers withdrew their consent before the completion of the study, and 6 mothers traveled out of the study area and did not return before the completion of the study
Selective reporting (reporting bias)	Low risk	All outcomes were predefined and reported.
Other bias	Low risk	The trial appears to be free of industry sponsorship.

Quiambao 2003

Methods	The study was a randomized, controlled trial.	
Participants	Country: Philippines. Number: 106 women in the intervention group and 54 women in the control group Mean age: 26.8 years. Mean gestational age: 27.3 weeks.	
Interventions	23-valent pneumococcal polysaccharide vaccine.	
Outcomes	Neonatal antibody levels (GM).	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details were not reported.
Allocation concealment (selection bias)	Unclear risk	Details were not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lack of blinding would be unlikely to affect results.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Lack of blinding would be unlikely to affect results.
Incomplete outcome data (attrition bias) All outcomes	High risk	Cord blood was obtained from 42/54 in the control group and 82/106 in the intervention group
Selective reporting (reporting bias)	Low risk	All outcomes were predefined and reported.
Other bias	Low risk	The trial appears to be free of industry sponsorship.

Shahid 1995

Methods	The study was a prospective double-blind controlled trial.	
Participants	Country: Bangladesh. Number: 36 women in the intervention group and 34 women in the control group Mean age: 25.6 years. Mean gestational age: 32.3 weeks.	

Shahid 1995 (Continued)

Interventions	23-valent pneumococcal polysaccharide vaccine vs meningococcal vaccine	
Outcomes	Maternal antibody levels (GM). Incidence of tenderness at the injection site.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details were not reported.
Allocation concealment (selection bias)	Unclear risk	Details were not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “double blind”.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “double blind”.
Incomplete outcome data (attrition bias) All outcomes	High risk	7/36 missing from intervention group; 10/34 missing from control group
Selective reporting (reporting bias)	Low risk	All outcomes were predefined and reported.
Other bias	Low risk	The trial appears to be free of industry sponsorship.

Zaman 2008

Methods	The study was a prospective, controlled, blinded, randomized trial	
Participants	Country: Bangladesh. Number: 168 women in the intervention group and 172 women in the control group Mean age: 24.9 years. Mean gestational age: data not available.	
Interventions	23-valent pneumococcal polysaccharide vaccine vs influenza vaccine	
Outcomes	Incidence of neonatal influenza. Incidence of maternal influenza. Percentage of mothers with seroprotection.	

Notes	The main purpose of the trial was to assess the effectiveness of influenza vaccine	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomization sequence was computer-generated.
Allocation concealment (selection bias)	Low risk	The randomization sequentially numbered opaque envelopes with data regarding assignments to study groups were provided to each clinic
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the mother-infant pairs, 316 were observed for the full 24-week period
Selective reporting (reporting bias)	Low risk	All outcomes were predefined and reported.
Other bias	Low risk	The trial appears to be free of industry sponsorship and the conflict of interest was declared

GM: geometric mean

vs: versus

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Daly 2003	The objective of this pilot study was to estimate enrolment rate for the phase III trial, not for the determination of the effectiveness of maternal immunization
Glezen 2000	It was an abstract only and there was not enough information in the abstract

Characteristics of ongoing studies *[ordered by study ID]*

Dunbar 2007

Trial name or title	PneuMum.
Methods	Randomized controlled trial.
Participants	Country: Australia. Number: 210 women aged 18-39 years who have an uncomplicated pregnancy: 70 women will receive pneumococcal vaccine in the third trimester; 70 at delivery; and 70 at 7 months after childbirth (the control group)
Interventions	23-valent pneumococcal polysaccharide vaccine.
Outcomes	Incidence of neonatal otitis media. Incidence of neonatal pneumococcal colonization. Neonatal antibody levels.
Starting date	2007.
Contact information	melissa.dunbar@menzies.edu.au.
Notes	

DATA AND ANALYSES

Comparison 1. Pneumococcal vaccine versus control vaccine

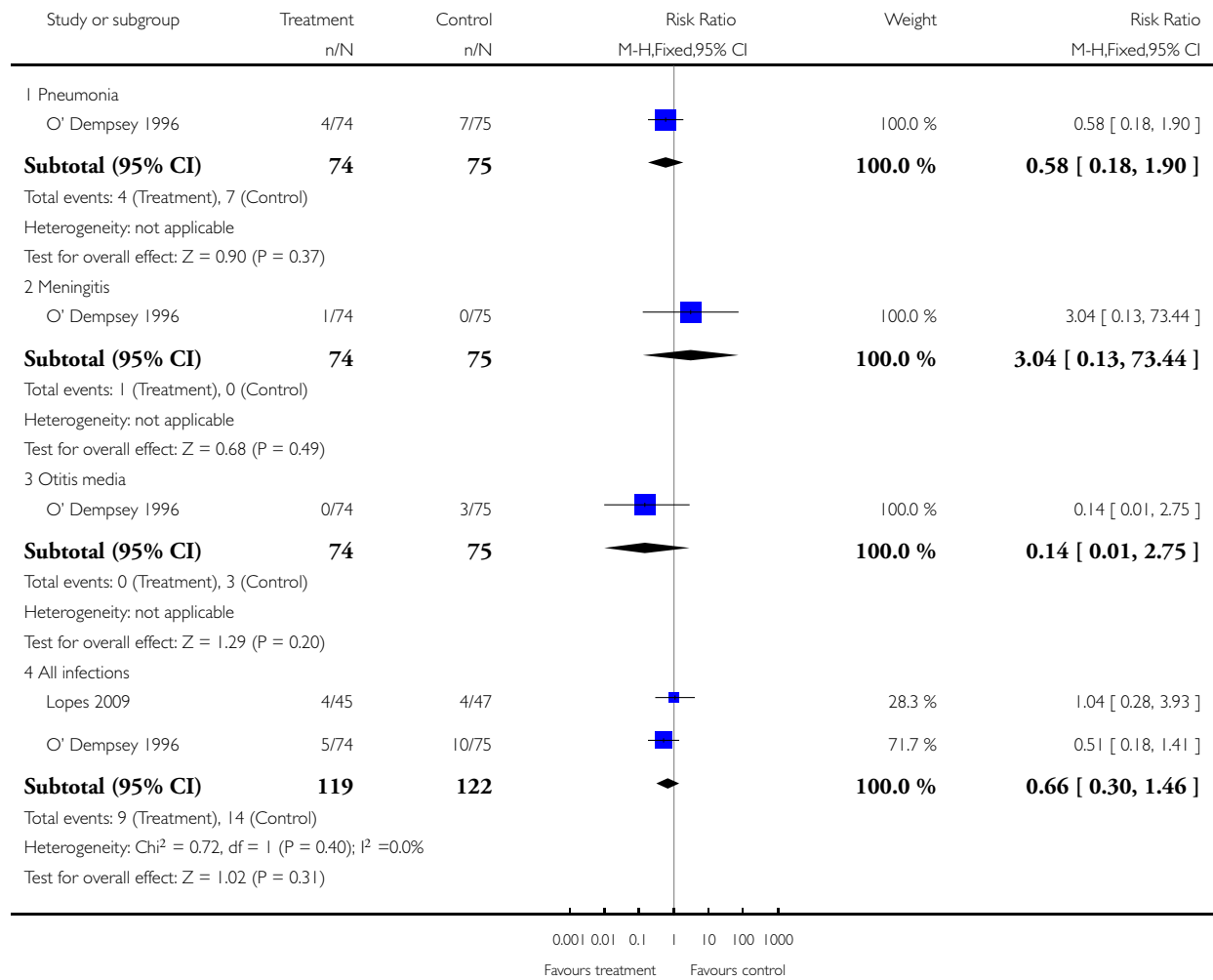
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neonatal infection	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Pneumonia	1	149	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.18, 1.90]
1.2 Meningitis	1	149	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [0.13, 73.44]
1.3 Otitis media	1	149	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.75]
1.4 All infections	2	241	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.30, 1.46]
2 Pneumococcal colonization	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 At 2-3 months of age	2	146	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.46, 2.78]
2.2 By 6-7 months of age	2	148	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.22, 2.08]
2.3 By 16 months of age	1	56	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.11, 0.98]
2.4 Serotype 6	1	92	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.01, 2.09]
2.5 Serotype 14	1	92	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.6 Serotype 19	1	92	Risk Ratio (M-H, Random, 95% CI)	2.09 [0.40, 10.85]
3 Neonatal antibody levels at birth			Other data	No numeric data
3.1 Serotype 6			Other data	No numeric data
3.2 Serotype 14			Other data	No numeric data
3.3 Serotype 19			Other data	No numeric data
4 Maternal antibody levels post vaccination			Other data	No numeric data
4.1 Serotype 6			Other data	No numeric data
4.2 Serotype 14			Other data	No numeric data
4.3 Serotype 19			Other data	No numeric data
5 Percentage of mothers with seroprotection	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Serotype 6 at delivery	1	340	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [1.31, 1.69]
5.2 Serotype 14 at delivery	1	340	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.25, 1.56]
5.3 Serotype 19 at delivery	1	340	Risk Ratio (M-H, Fixed, 95% CI)	2.29 [1.89, 2.76]
5.4 Serotype 6 at 12 months post-delivery	1	340	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [1.00, 1.12]
5.5 Serotype 14 at 12 months post-delivery	1	340	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.98, 1.15]
5.6 Serotype 19 at 12 months post-delivery	1	340	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.37, 1.85]
6 Adverse maternal effects	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Tenderness at the injection site	2	130	Risk Ratio (M-H, Random, 95% CI)	3.20 [0.32, 31.54]

Analysis 1.1. Comparison 1 Pneumococcal vaccine versus control vaccine, Outcome 1 Neonatal infection.

Review: Pneumococcal vaccination during pregnancy for preventing infant infection

Comparison: 1 Pneumococcal vaccine versus control vaccine

Outcome: 1 Neonatal infection

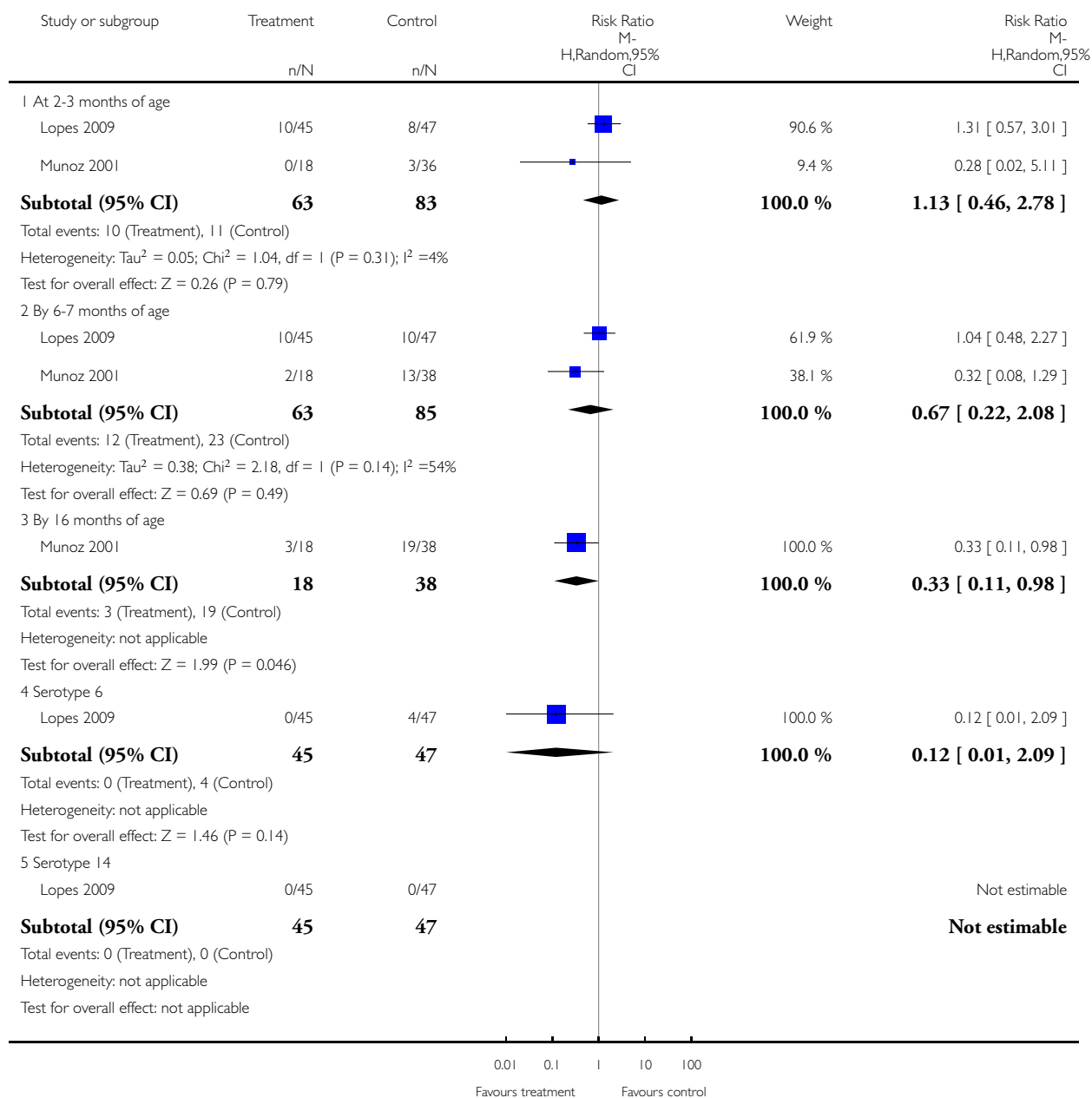


Analysis 1.2. Comparison 1 Pneumococcal vaccine versus control vaccine, Outcome 2 Pneumococcal colonization.

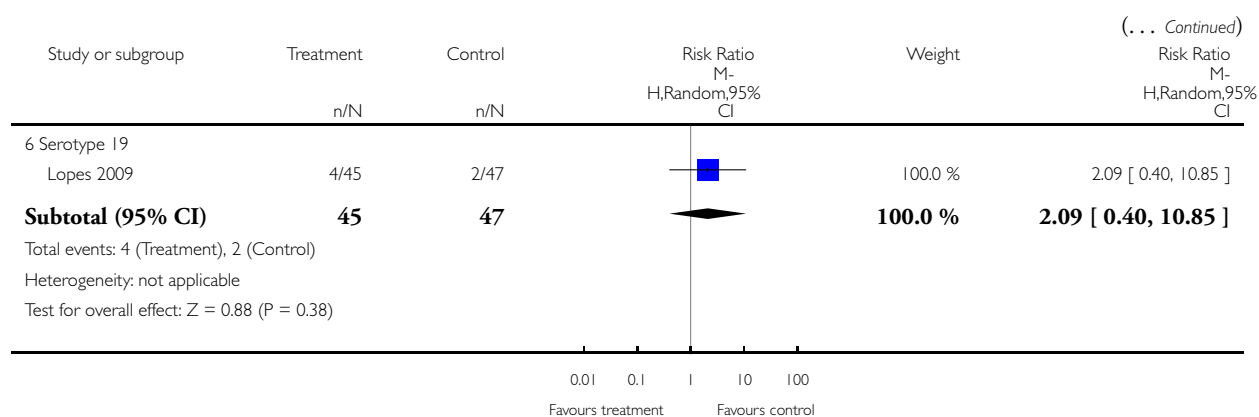
Review: Pneumococcal vaccination during pregnancy for preventing infant infection

Comparison: 1 Pneumococcal vaccine versus control vaccine

Outcome: 2 Pneumococcal colonization



(Continued ...)



Analysis 1.3. Comparison 1 Pneumococcal vaccine versus control vaccine, Outcome 3 Neonatal antibody levels at birth.

Neonatal antibody levels at birth

Study	Treatment N	Treatment IgG GM	Treatment 95% CI	Control N	Control IgG GM	Control 95% CI
Serotype 6						
Munoz 2001	20	3.7	2.6 to 5.3	40	1.1	0.8 to 1.5
O' Dempsey 1996	43	2.7	1.7 to 4.4	26	5.7	2.9 to 11.3
Quiambao 2003	82	5.3	4.0 to 7.1	42	0.87	0.58 to 1.3
Serotype 14						
Munoz 2001	19	13.4	7.3 to 25.1	39	3.0	2.2 to 3.9
O' Dempsey 1996	41	13.1	8.6 to 20.0	23	7.1	3.7 to 13.3
Quiambao 2003	82	8.1	6.1 to 10.7	42	2.4	1.6 to 3.7
Serotype 19						
Munoz 2001	19	3.6	2.3 to 5.6	39	1.5	1.1 to 2.1
O' Dempsey 1996	43	4.1	2.7 to 5.9	24	3.6	1.8 to 7.3

Neonatal antibody levels at birth (Continued)

Quiambao 2003	82	21.9	15.2 to 31.6	42	3.9	2.5 to 6.1

Analysis 1.4. Comparison 1 Pneumococcal vaccine versus control vaccine, Outcome 4 Maternal antibody levels post vaccination.

Maternal antibody levels post vaccination

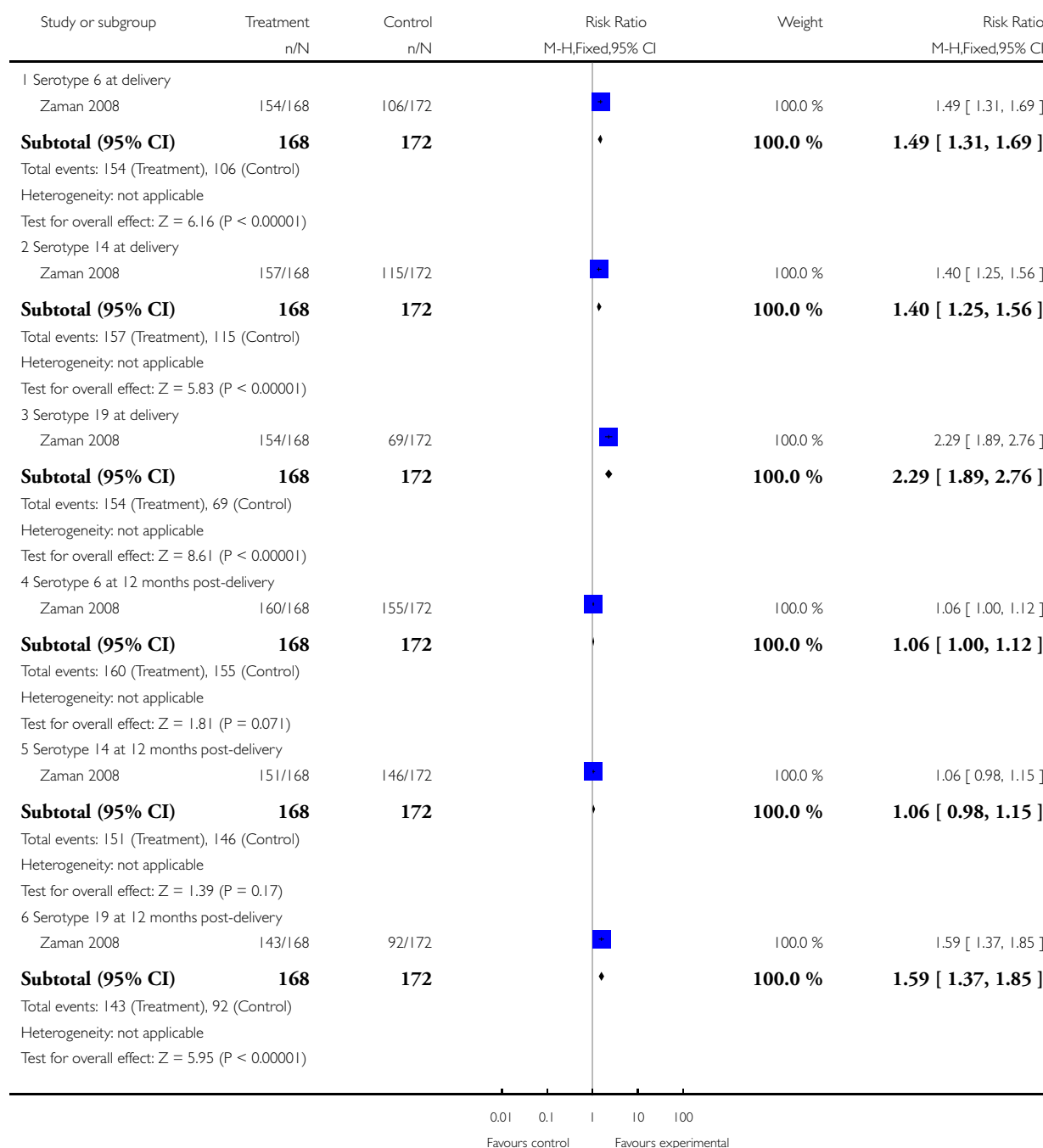
Study	Treatment N	Treatment IgG GM	Treatment 95% CI	Control N	Control IgG GM	Control 95% CI
Serotype 6						
Munoz 2001	20	4.4	2.7 - 7.1	40	0.9	0.6 - 1.3
O' Dempsey 1996	49	7.3	4.4 - 12.0	26	14.4	6.4 - 32.7
Shahid 1995	29	13.8	NA	24	5.3	NA
Serotype 14						
Munoz 2001	20	16.8	8.0 - 35.5	40	3.0	2.2 - 4.0
O' Dempsey 1996	49	43.1	39.5 - 70.6	26	18.8	9.2 - 38.8
Serotype 19						
Munoz 2001	20	3.7	2.3 - 6.0	40	1.4	1.0 - 1.9
O' Dempsey 1996	49	11.8	7.7 - 18.2	26	10.3	4.3 - 25.2
Shahid 1995	29	17.4	NA	24	4.7	NA

Analysis 1.5. Comparison 1 Pneumococcal vaccine versus control vaccine, Outcome 5 Percentage of mothers with seroprotection.

Review: Pneumococcal vaccination during pregnancy for preventing infant infection

Comparison: 1 Pneumococcal vaccine versus control vaccine

Outcome: 5 Percentage of mothers with seroprotection

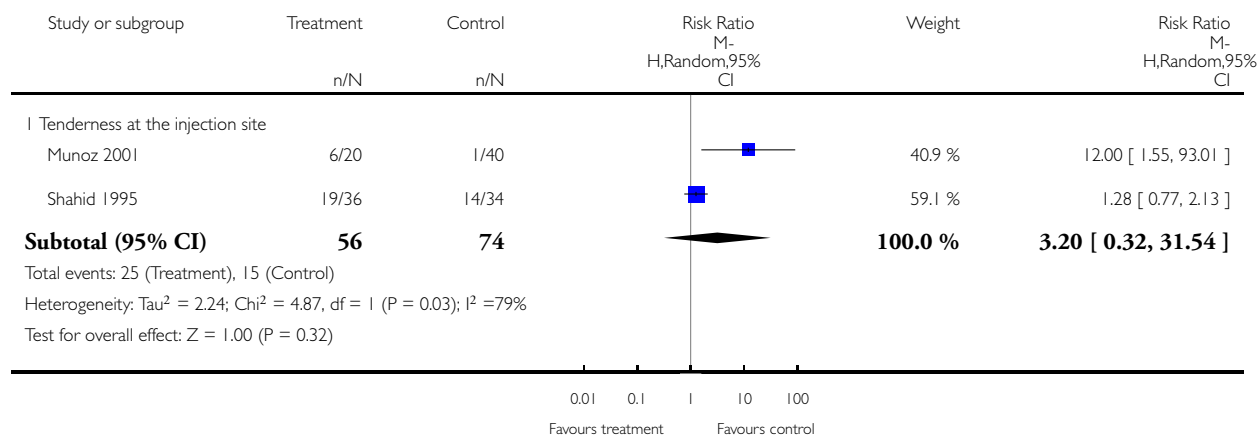


Analysis 1.6. Comparison 1 Pneumococcal vaccine versus control vaccine, Outcome 6 Adverse maternal effects.

Review: Pneumococcal vaccination during pregnancy for preventing infant infection

Comparison: 1 Pneumococcal vaccine versus control vaccine

Outcome: 6 Adverse maternal effects



APPENDICES

Appendix 1. Search strategy

In the initial version of the review, we searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2004, Issue 2), MEDLINE (January 1966 to June 2004) and EMBASE (January 1985 to June 2004).

CENTRAL (*The Cochrane Library* 2004, Issue 2)

#1 PREGNANCY*:ME

#2 PREGNAN*

#3 MATERN*

#4 ANTEPART*

#5 PRENATAL

#6 ANTENATAL

#7 PERINATAL

#8 ((((((#1 or #2) or #3) or #4) or #5) or #6) or #7)

#9 PNEUMOCOCC*

#10 PNEUMOCOCCAL*:ME

#11 (#9 or #10)

#12 VACCIN*

#13 VACCINE*:ME

#14 IMMUNIZATION*:ME

#15 ((#12 or #13) or #14)

#16 (#11 and #15)

#17 (#8 and #16)

We adapted the above search strategy to search MEDLINE (January 1966 to June 2004) and EMBASE (January 1985 to June 2004) by selecting appropriate MeSH and/or keywords from their respective thesauri.

WHAT'S NEW

Last assessed as up-to-date: 30 September 2014.

Date	Event	Description
30 September 2014	New citation required but conclusions have not changed	Review updated.
30 September 2014	New search has been performed	Search updated. Seven new reports were identified. All of them reported new information for two included studies (Lopes 2009 ; Zaman 2008). Data from the new reports were added. A 'Summary of findings' table has been incorporated

HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 1, 2006

Date	Event	Description
31 December 2011	New search has been performed	Search updated. One new trial identified (Zaman 2008) and included. Trial reports previously awaiting classification, have now been incorporated into the review as two new included studies (Lopes 2009 ; Obaro 2004) and one ongoing study (Dunbar 2007). One study, previously classified as excluded (Quiambao 2003) has now been included. This updated review is now comprised of seven included studies, two excluded studies and one ongoing study

(Continued)

31 December 2011	New citation required but conclusions have not changed	For this update we have added two new included studies. The overall results and conclusions have not changed
31 December 2011	New search has been performed	Updated search, adding two included studies.
6 July 2011	Amended	Search updated. Eight reports added to Studies awaiting classification (Deubzer 2004; Dunbar 2007a; Henkle 2010; Holmlund 2011; Lopes 2009a; Obaro 2004a; Quiambao 2007; Steinhoff 2010)
8 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Surasith Chaithongwongwatthana (SC) designed the review and wrote the protocol. Waralak Yamasmit (WY), Sompop Limpongsanurak (SL), Pisake Lumbiganon (PL), and Jorge Tolosa (JT) provided general advice and approved the published version. SC and WY conducted and drafted the review. SL, PL, and JT gave intellectual comments on the review and approved the final version.

For the 2014 update, SC and WY contributed to data extraction and assessment of risk of bias in studies. SC conducted data analysis and updated the main text. The final version of the updated review was approved by all review authors.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Chulalongkorn University, Thailand.
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External sources

- Thailand Research Fund (Senior Research Scholar), Thailand.
- UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research (RHR), World Health Organization, Switzerland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For the initial version of the review, we searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2004 Issue 2), MEDLINE (January 1966 to June 2004) and EMBASE (January 1985 to June 2004). This additional searching has not been carried out for this update.

The outcomes have been separated into 'Primary' and 'Secondary' outcomes and the methods have been updated to reflect the latest *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

INDEX TERMS

Medical Subject Headings (MeSH)

Gestational Age; Pneumococcal Infections [immunology; *prevention & control]; Pneumococcal Vaccines [*administration & dosage]; Randomized Controlled Trials as Topic; Vaccination [*methods]

MeSH check words

Female; Humans; Infant; Infant, Newborn; Pregnancy



Cochrane
Library

Cochrane Database of Systematic Reviews

Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes (Review)

Buppasiri P, Lumbiganon P, Thinkhamrop J, Ngamjarus C, Laopaiboon M, Medley N

Buppasiri P, Lumbiganon P, Thinkhamrop J, Ngamjarus C, Laopaiboon M, Medley N.

Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes.

Cochrane Database of Systematic Reviews 2015, Issue 2. Art. No.: CD007079.

DOI: 10.1002/14651858.CD007079.pub3.

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	3
BACKGROUND	5
OBJECTIVES	5
METHODS	5
RESULTS	9
Figure 1.	11
Figure 2.	12
Figure 3.	14
DISCUSSION	18
AUTHORS' CONCLUSIONS	19
ACKNOWLEDGEMENTS	19
REFERENCES	20
CHARACTERISTICS OF STUDIES	25
DATA AND ANALYSES	69
Analysis 1.1. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 1 Preterm birth (a) Birth prior to 37 weeks.	72
Analysis 1.2. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 2 Preterm birth (a) Birth prior to 37 weeks by dose of calcium.	74
Analysis 1.3. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 3 Preterm birth (a) Birth prior to 37 weeks by started to take calcium.	75
Analysis 1.4. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 4 Preterm birth (a) Birth prior to 37 weeks by type of calcium.	76
Analysis 1.5. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 5 Preterm birth (b) Birth prior to 34 weeks.	77
Analysis 1.6. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 6 Preterm birth (b) Birth prior to 34 weeks - Sensitivity analysis by concealment allocation.	78
Analysis 1.7. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 7 Maternal weight gain (g/w).	79
Analysis 1.8. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 8 Maternal bone mineral density (g/cm2) - First phalanx (calcium 300 mg).	79
Analysis 1.9. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 9 Maternal bone mineral density (g/cm2) - Second metacarpal (calcium 300 mg).	80
Analysis 1.10. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 10 Maternal bone mineral density (g/cm2) - Fourth metacarpal (calcium 300 mg).	80
Analysis 1.11. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 11 Maternal bone mineral density (g/cm2) - First phalanx (calcium 600 mg).	81
Analysis 1.12. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 12 Maternal bone mineral density (g/cm2) - Second metacarpal (calcium 600 mg).	81
Analysis 1.13. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 13 Maternal bone mineral density (g/cm2) - Fourth metacarpal (calcium 600 mg).	82
Analysis 1.14. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 14 Maternal death.	82
Analysis 1.15. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 15 Maternal admission to intensive care unit.	83
Analysis 1.16. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 16 Vaginal birth.	84
Analysis 1.17. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 17 Instrumental vaginal birth.	85

Analysis 1.18. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 18 Caesarean section.	86
Analysis 2.1. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 1 Low birthweight (< 2500 g).	87
Analysis 2.2. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 2 Low birthweight (< 2500 g) by started to take calcium.	88
Analysis 2.3. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 3 Low birthweight (< 2500 g) by type of calcium.	89
Analysis 2.4. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 4 Birthweight (g).	90
Analysis 2.5. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 5 Perinatal mortality.	91
Analysis 2.6. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 6 Stillbirth or fetal death.	92
Analysis 2.7. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 7 Admission to neonatal intensive care unit.	93
Analysis 2.8. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 8 Birth length (cm).	94
Analysis 2.9. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 9 Head circumference (cm).	95
Analysis 2.10. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 10 Intrauterine growth restriction.	96
Analysis 2.11. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 11 Neonatal bone mineral density (g/cm ²).	97
Analysis 3.1. Comparison 3 Calcium supplementation versus placebo or no treatment (adverse outcomes), Outcome 1 Side effects of calcium supplementation - Maternal cholestatic jaundice.	98
Analysis 3.2. Comparison 3 Calcium supplementation versus placebo or no treatment (adverse outcomes), Outcome 2 Urinary stones.	99
Analysis 3.3. Comparison 3 Calcium supplementation versus placebo or no treatment (adverse outcomes), Outcome 3 Urinary tract infection.	100
Analysis 3.4. Comparison 3 Calcium supplementation versus placebo or no treatment (adverse outcomes), Outcome 4 Renal colic.	100
Analysis 3.5. Comparison 3 Calcium supplementation versus placebo or no treatment (adverse outcomes), Outcome 5 Impaired renal function.	101
Analysis 3.6. Comparison 3 Calcium supplementation versus placebo or no treatment (adverse outcomes), Outcome 6 Maternal anemia.	102
ADDITIONAL TABLES	102
WHAT'S NEW	103
CONTRIBUTIONS OF AUTHORS	103
DECLARATIONS OF INTEREST	103
SOURCES OF SUPPORT	104
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	104
INDEX TERMS	104

Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

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ABSTRACT

Background

Maternal nutrition during pregnancy is known to have an effect on fetal growth and development. It is recommended that women increase their calcium intake during pregnancy and lactation, although the recommended dosage varies among professionals. Currently, there is no consensus on the role of routine calcium supplementation for pregnant women other than for preventing or treating hypertension.

Objectives

To determine the effect of calcium supplementation on maternal, fetal and neonatal outcomes (other than for preventing or treating hypertension) as well as any possible side effects.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30th September 2014).

Selection criteria

We considered all published, unpublished and ongoing randomised controlled trials (RCTs) comparing maternal, fetal and neonatal outcomes in pregnant women who received calcium supplementation versus placebo or no treatment. Cluster-RCTs were eligible for inclusion but none were identified. Quasi-RCTs and cross-over studies were not eligible for inclusion.

Data collection and analysis

Two review authors independently assessed trials for inclusion and risk of bias, extracted data and checked them for accuracy.

Main results

Twenty-five studies met the inclusion criteria, but only 23 studies contributed data to the review. These 23 trials recruited 18,587 women, with 17,842 women included in final analyses. There were no statistically significant differences between women who received calcium supplementation and those who did not in terms of reducing preterm births less than 37 weeks' gestation (risk ratio (RR) 0.86, 95% confidence interval (CI) 0.70 to 1.05; 13 studies, 16,139 women; random-effects model) or less than 34 weeks' gestation (RR 1.04, 95% CI 0.80 to 1.36; four trials, 5669). Most studies were of low risk of bias. We conducted sensitivity analysis for the outcome of preterm birth less than 37 weeks by removing two trials with unclear risk of bias for allocation concealment; the results then favoured treatment with calcium supplementation (RR 0.80, 95% CI 0.65 to 0.99; 11 trials, 15,379 women). There was no significant difference in infant low birthweight between the two treatment groups (RR 0.93, 95% CI 0.81 to 1.07; six trials, 14,162 infants; random-effects model). However, when compared to the control group, women in the calcium supplementation group gave birth to slightly heavier birthweight infants (mean difference 56.40, 95% CI 13.55 to 99.25; 21 trials, 9202 women; random-effects model).

Three outcomes were chosen for assessment with the GRADE software: preterm birth less than 37 weeks; preterm birth less than 34 weeks; and low birthweight less than 2500 g. Evidence for these outcomes was assessed as of moderate quality.

Authors' conclusions

This review indicates that there are no clear additional benefits to calcium supplementation in prevention of preterm birth or low infant birthweight. While there was a statistically significant difference of 56 g identified in mean infant birthweight, there was significant heterogeneity identified, and the clinical significance of this difference is uncertain.

PLAIN LANGUAGE SUMMARY

Effect of taking extra calcium (other than preventing or treating high blood pressure) during pregnancy for improving maternal and infant health

Maternal nutrition during pregnancy is known to have a significant effect on fetal growth and development. In our review, regular intake of extra calcium tablets during pregnancy did not improve the number of preterm births or other infant outcomes, except for a slight increase in infant birthweight in the group of women who received calcium supplementation. Most studies included in this review were assessed as of low risk of bias, and evidence for specific outcomes was graded as of moderate quality. Taking calcium supplementation did not appear to have any obvious side effects. Our review included 25 randomised controlled studies, but only 23 studies involving 18,587 women contributed outcome data. The majority of the evidence was based on fewer numbers of studies.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Calcium supplementation versus placebo or no treatment for improving pregnancy and infant outcomes						
Patient or population: healthy pregnant women receiving calcium supplementation vs placebo or no treatment Settings: trials located in Australia, Guatemala, India (3), Iran, and the USA (3). A multi-centre study took place in Argentina, Egypt, India, Peru, South Africa, United Kingdom and Vietnam. Intervention: calcium supplementation versus placebo or no treatment (maternal outcomes)						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Calcium supplementation versus placebo or no treatment (maternal outcomes)				
Preterm birth (a) Birth prior to 37 weeks	Study population		RR 0.86 (0.7 to 1.05)	16139 (13 studies)	⊕⊕⊕○ moderate ¹	We conducted sensitivity analysis by removing 2 trials with unclear risk of bias for allocation concealment; the results then favoured treatment with calcium supplementation (RR 0.80, 95% CI 0.65 to 0.99; 11 trials, 15379 women)
	105 per 1000	90 per 1000 (73 to 110)				
	Moderate					
	100 per 1000	86 per 1000 (70 to 105)				
Preterm birth (b) Birth prior to 34 weeks	Study population		RR 1.04 (0.8 to 1.36)	5669 (4 studies)	⊕⊕⊕○ moderate ¹	
	36 per 1000	38 per 1000 (29 to 49)				
	Moderate					
	30 per 1000	31 per 1000 (24 to 41)				

Low birthweight (<2500 g)	Study population		RR 0.93 (0.81 to 1.07)	14162 (6 studies)	⊕⊕⊕○ moderate ²
	116 per 1000	108 per 1000 (94 to 125)			
	Moderate				
	86 per 1000	80 per 1000 (70 to 92)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Wide confidence interval crossing the line of no effect. (-1)

² Statistical heterogeneity ($I^2 > 60\%$). (-1)

BACKGROUND

Description of the condition

Calcium metabolism

Calcium is an essential mineral for many of the body's processes (Trichopoulos 1990). Calcium is a key and important intracellular component for maintaining cell membranes, and has a role in nerve cell function, muscle contraction, enzyme and hormone actions, and is essential for bone mineralisation. Maternal nutrition during pregnancy has a significant effect on fetal growth and development (Luke 1994; Susser 1991). Calcium is transported across the placenta by an active transport process, and is important in many developmental functions, including skeletal development (McGuire 2007).

During pregnancy and lactation women require an increase in their calcium intake (Cross 1995; Ritchie 1998). This is not only to maintain maternal calcium balance and bone density, but also to meet the demands of the growing fetus/infant.

Description of the intervention

Calcium supplementation

The recommendations for calcium intake during pregnancy and lactation vary from 600 mg to 1425 mg per day, up to 600 mg higher than in non-pregnant women (Prentice 1994). Approximately 200 mg of calcium per day is secreted into breast milk (Prentice 1994).

The increase in calcium requirements may be met through dietary intake. However, supplementation of calcium during pregnancy and lactation has been recommended by some, at doses between 300 mg and 2000 mg per day (Belizan 1991; Koo 1999; Raman 1978). For this review, we have arbitrarily divided calcium supplementation into low dose (less than 1000 mg per day) and high dose (1000 mg or more per day) (Jarjou 2006; Kalkwarf 1997; Prentice 1995; Raman 1978; Villar 1990).

Calcium tablets are inexpensive and readily available. However, side effects have been reported, including difficulty in swallowing, an increase in urinary stones and urinary tract infection, as well as reduced absorption of other minerals such as iron, zinc and magnesium (Hallberg 1992; McGuire 2007).

The effect of calcium supplementation on weight is unclear, with some studies identifying a reduction in body weight, possibly through the combination of calcium with fatty acids which are subsequently not absorbed by the body (Heaney 2002; Sampath 2008; Trowman 2006; Yanovski 2009).

How the intervention might work

During pregnancy and lactation, maternal bone mineral density decreases in multiple sites of the body such as the lumbar spine, femoral neck, hip and wrist. However, this is quickly reversed after cessation of breastfeeding (Cross 1995; Kalkwarf 1997; Laskey 1999; Prentice 1995; Sowers 1993; Sowers 1995). Inadequate intake of calcium may harm both the woman and her fetus. Maternal risks of inadequate calcium intake include osteopenia, osteoporosis, tremor, paraesthesia, muscle cramps and tetany (muscle spasm and twitching). Potential problems for the fetus/infant include delayed fetal growth, low birthweight and poor bone mineralisation (Inzucchi 1999; Koo 1999). It is unclear whether calcium supplementation may help women and babies avoid the complications associated with inadequate calcium intake.

Why it is important to do this review

Current approach to calcium supplementation in pregnancy

Currently, there is no consensus on the role of routine calcium supplementation for pregnant women.

A Cochrane review evaluating calcium supplementation for the prevention of pre-eclampsia identified a significant beneficial effect, almost halving the risk of women developing pregnancy-induced hypertension (Hofmeyr 2014). However, the effect of calcium supplementation on other pregnancy and infant outcomes remains uncertain, with some studies identifying a beneficial effect on fetal growth and bone mineralisation (Chan 2006; Chang 2003; Janakiraman 2003), although this is not universal (Jarjou 2006; Prentice 1995). Calcium also plays a role in smooth muscle function, being important in muscle contraction. Some studies have suggested that calcium supplementation may contribute to altered muscle tone and may therefore contribute to the risk of preterm birth (Hofmeyr 2014), although the precise effect is unclear (Belizan 1991; Carroli 1994; Lopez-Jaramillo 1989; Villar 1990; Villar 1998). While there is a clear benefit of calcium supplementation in the prevention of hypertension during pregnancy, the effect on other outcomes requires further evaluation.

OBJECTIVES

To determine the effect of calcium supplementation on maternal, fetal and neonatal outcomes (other than for preventing or treating hypertension), including the occurrence of side effects.

METHODS

Criteria for considering studies for this review

Types of studies

We included all published, unpublished and ongoing simple and randomised controlled trials (RCTs) comparing maternal, fetal, and neonatal outcomes in pregnant women who received calcium supplementation compared with placebo or no treatment. Cluster-RCTs were eligible for inclusion but none were identified. Quasi-RCTs and cross-over studies were not eligible for inclusion.

Types of participants

Pregnant women who received any calcium supplementation compared with placebo or no treatment.

Types of interventions

Calcium supplementation during pregnancy compared with placebo or no treatment.

Types of outcome measures

Primary outcomes

Maternal outcomes

1. Preterm birth less than 37 weeks' gestation

Infant outcomes

1. Low birthweight (less than 2500 g)

Secondary outcomes

Maternal outcomes

1. Preterm birth less than 34 weeks' gestation
2. Maternal weight gain
3. Maternal bone mineral density (BMD) measured by dual-energy x-ray absorptiometry (osteopenia is classified as BMD between -1 and -2.5 SD; osteoporosis is classified as BMD less than -2.5 SD)
4. Leg cramps
5. Backache
6. Tetany
7. Incidence of fracture
8. Duration of breastfeeding
9. Tremor
10. Paraesthesia
11. Mother admitted to an intensive care unit
12. Maternal death

13. Mode of birth (vaginal birth, Instrumental vaginal birth, caesarean section)
14. Postpartum haemorrhage

Fetal and neonatal outcomes

1. Stillbirth or fetal death (fetus died in uterus after 20 weeks' gestation or during labour and delivery)
2. Neonatal death (baby died in first 28 days of life)
3. Perinatal mortality (stillbirth and neonatal death)
4. Admission to neonatal intensive care unit
5. Birthweight
6. Birth length
7. Head circumference
8. Intrauterine growth restriction
9. Neonatal BMD (measured by single-photon absorptiometry or dual-energy x-ray absorptiometry)
10. Osteopenia
11. Rickets
12. Fracture

Adverse outcomes

1. Side effects of calcium supplementation
2. Compliance
3. Satisfaction (as defined by the trial authors)
4. Urinary stones
5. Urinary tract infection
6. Nephrocalcinosis
7. Impaired renal function (as defined by the trial authors)
8. Maternal anaemia (as defined by the trial authors)

Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (30 September 2014).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We did not apply any language or date restrictions.

Data collection and analysis

For methods used in the previous version of this review, *see* [Buppasiri 2011](#).

For this update, the following methods were used for assessing the 19 reports that were identified as a result of the updated search. The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted the third review author.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted the third review author. Data were entered into Review Manager software ([RevMan 2014](#)) and checked for accuracy.

When information regarding any of the above was unclear, we planned to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). Any disagreement was resolved by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes.

Where sufficient information was reported, or could be supplied by the trial authors, we planned to re-include missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we had about other possible sources of bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we planned to assess the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. In future updates, we will explore the impact of the level of bias through undertaking sensitivity analyses - see [Sensitivity analysis](#).

For this update the quality of the evidence was assessed using the GRADE approach (Schunemann 2009). We assessed the quality of the body of evidence relating to the following outcomes.

1. Preterm birth < 37 weeks
2. Preterm birth < 34 weeks
3. Low birthweight (< 2500 g)

GRADE profiler (GRADEpro 2014) was used to import data from Review Manager 5.3 (RevMan 2014) and create a 'Summary of findings' table, or a summary of the intervention effect and a measure of quality for each of the above outcomes. The GRADE

approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

We used the mean difference as outcomes were measured in the same way between trials. In future updates, we may use the standardised mean difference to combine trials that measure the same outcome but use different methods.

Unit of analysis issues

Cluster-randomised trials

We have not included any cluster-randomised trials in this update. If in future updates we include cluster-randomised trials in the analyses, we will adjust their sample sizes using the methods described in the *Handbook* [Section 16.3.4 or 16.3.6] using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Cross-over trials

We have not included cross-over trials in this review and do not consider this design appropriate to answer the review's questions.

Other unit of analysis issues

We have not included multiple pregnancies in this review because multiple pregnancies may have an effect on the outcomes of interest, such as preterm birth, and so studies including multiple pregnancies are not considered eligible for inclusion.

In studies that had more than two treatment groups, we divided the placebo arm between the two treatment arms. Specifically, for the trial [Belizan 1983](#), in [Analysis 2.4](#) and [Analysis 2.9](#), the placebo arm was halved to enable inclusion of data for treatment groups one and two.

Dealing with missing data

For included studies, levels of attrition were noted. In future updates, if more eligible studies are included, the impact of including studies with high levels of missing data in the overall assessment of treatment effect will be explored by using sensitivity analysis. For all outcomes, analyses were carried out, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the τ^2 , I^2 and χ^2 statistics. We regarded heterogeneity as substantial if an I^2 was greater than 30% and either the τ^2 was greater than zero, or there was a low P value (less than 0.10) in the χ^2 test for heterogeneity. When we identified substantial heterogeneity (above 30%), we explored it by performing pre-specified subgroup analysis.

Assessment of reporting biases

Where there were 10 or more studies in the meta-analysis we investigated reporting biases (such as publication bias) using funnel plots. We assessed funnel plot asymmetry visually. If asymmetry was suggested by a visual assessment, we performed exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software ([RevMan 2014](#)). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar.

If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. The

random-effects summary was treated as the average range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we did not combine trials. Where we used random-effects analyses, the results were presented as the average treatment effect with 95% confidence intervals, and the estimates of τ^2 and I^2 .

Subgroup analysis and investigation of heterogeneity

Where we identified substantial heterogeneity, we investigated it using subgroup analyses and sensitivity analyses. We considered whether an overall summary was meaningful, and if it was, we used random-effects analysis to produce it.

We carried out the following subgroup analyses for maternal primary outcomes.

1. Preterm birth < 37 weeks by dose of calcium (low dose or less than 1000 mg/day versus high dose or 1000 mg/day or more)
2. Preterm birth < 37 weeks by gestational week started to take calcium (before 20 weeks versus 20 weeks or more)
3. Preterm birth < 37 weeks by type of calcium (carbonate versus lactate versus gluconate)

We carried out the following subgroup analyses for Infant primary outcomes.

1. Low birthweight < 2500 g by gestational week started to take calcium (before 20 weeks versus 20 weeks or more)
2. Low birthweight < 2500 g by type of calcium (gluconate versus carbonate)

We assessed subgroup differences by interaction tests available within RevMan ([RevMan 2014](#)). We reported the results of subgroup analyses quoting the χ^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We planned to carry out the following sensitivity analysis to explore the effect of trial quality assessed by concealment of allocation, with poor quality studies being excluded from the analyses in order to assess whether this makes any difference to the overall result.

1. Preterm birth < 37 weeks (adequate allocation concealment versus unclear or no allocation concealment)
2. Preterm birth < 34 weeks (adequate allocation concealment versus unclear or no allocation concealment)
3. Low birthweight (< 2500 g)

We conducted the above sensitivity analysis, apart from the low birthweight outcome because there were no trials at unclear or low risk of bias for allocation concealment contributing data to this outcome.

RESULTS

Description of studies

Results of the search

The original search yielded 72 trial reports (Buppasiri 2011). After exploring the contents and grouping for duplicates, we included data from 21 trials (54 reports). One further trial that was otherwise eligible for inclusion specifically focused on maternal blood lead levels and did not report any other outcomes, and so has not contributed data to the review (Ettinger 2009). We have provided details of this study in [Characteristics of included studies](#) but we have not referred to this study in the discussion of included studies below. We excluded 14 trials and four trials were 'Awaiting classification' because only the abstracts were available (Almirante 1998; Chames 2002; Galimberti 2001) - we tried to contact the authors but unfortunately full papers were not available.

For this update, a search in September 2014 identified another 19 reports for eligibility assessment. Three new trials were eligible for inclusion (Goldberg 2013; Herrera 2006; Kumar 2009). Four new reports (related to three trials), one of which requires translation (Zheng 2000), were abstracts and were added to [Studies awaiting classification](#). Six reports were excluded, three of which were duplicates for studies in awaiting classification (Almirante 1998; Chames 2002; Galimberti 2001) and have now been excluded because we have not had replies from authors at the second round of queries. Finally, six further new reports were additional publications for already included studies.

At this update, we now have 25 included studies (63 reports), but only 23 studies contribute outcome data (Herrera 2006 and Ettinger 2009 contribute no outcome data). There are 20 excluded studies (21 reports), and three abstracts that remain in [Studies awaiting classification](#) (we have attempted to contact authors but have had no replies). We should note that the newly included Goldberg 2013 reports on the same trial as the previously included Jarjou 2006. Jarjou 2006 analyses a subset of women and reports specific outcomes not included in the much later report on the full sample. We have kept these data separate for clarity.

Included studies

For more information about included studies, see: [Characteristics of included studies](#).

Design

All included studies were reported as randomised controlled trials (RCTs), and one trial (Villar 2006) was stratified by country.

Sample size

The total number of participants included in the 23 trials (of the 25 included trials) that contributed data to this review was 18,587 pregnant women, but only 17,842 were included in final analyses.

Ettinger 2009 and Herrera 2006 did not contribute to outcome data for this review. Missing data amounted to 4.01% overall (745 in 17,842). The sample size varied from 23 to 8325 participants per trial.

Setting

The 25 included trials took place in various countries: Argentina, Australia, Columbia, Egypt, Ecuador, Gambia, Guatemala, Hong Kong, India, Iran, Mexico, South Africa, United States and Vietnam.

Participants

This review includes data for 18,578 pregnant women. Three trials (Chan 2006; Herrera 2006; Villar 1990) included only adolescent pregnant women (309 women, mean age 17.0 years), but the remaining trials were not restricted to adolescents. Two trials (Jarjou 2006; Raman 1978) included only pregnant women from low socioeconomic groups. The largest study (Villar 2006 with 8325 women) recruited only pregnant women who received less than 600 mg dietary calcium per day. One study (Lopez-Jaramillo 1997) included pregnant women who had lived at an altitude of 2800 m for a period of at least one year. One study (Sanchez-Ramos 1994) enrolled pregnant women who had normotension but positive roll-over and angiotensin tests.

Interventions

Calcium supplementation was used in the treatment groups in all trials and compared with placebo or no treatment control groups. Various types of calcium were used such as calcium carbonate, calcium gluconate, calcium lactate and combined calcium. Calcium carbonate was prescribed in most studies (in 17 of the 23 trials). Calcium lactate was prescribed in one trial and calcium gluconate was prescribed in one trial. Combined calcium supplementation was prescribed in two trials and three trials did not specify the type of calcium used. For timing of calcium supplementation; 11 trials (Belizan 1991; Boggess 1997; Crowther 1999; Goldberg 2013; Jarjou 2006; Karandish 2003; Lopez-Jaramillo 1989; Purwar 1996; Sanchez-Ramos 1995; Taherian 2002; Villar 1990) started calcium supplementation at 20 weeks' gestational age (or after) until delivery. Five trials (Belizan 1983; Chan 2006; Kumar 2009; Levine 1997; Villar 2006) started calcium supplementation at gestational age less than 20 weeks until delivery. Timing was unclear in the remaining studies. For dosage of calcium, 14 trials (Belizan 1991; Boggess 1997; Crowther 1999; Goldberg 2013; Jarjou 2006; Karandish 2003; Kumar 2009; Levine 1997; Lopez-Jaramillo 1989; Purwar 1996; Sanchez-Ramos 1994; Sanchez-Ramos 1995; Villar 1990; Villar 2006) prescribed 1000 mg/d or more (range 1000 to 2000 mg/d). Three trials (Raman 1978; Rogers 1999; Taherian 2002) prescribed calcium less than 1000 mg/day (range 300 mg to 600 mg).

In the [Taherian 2002](#) study, calcium supplementation (Caltrate) was prescribed 600 mg at 22 to 32 weeks' gestational age and then 1200 mg from 32 weeks until delivery.

Outcomes

The primary outcomes or objectives of 16 of the 23 trials that contributed data to this review were incidence of pregnancy induced hypertension or changes in blood pressure, which were not relevant to this review. However, these studies also reported other outcome data relevant to this review, e.g. preterm birth, maternal weight gain, gestational age, birthweight, birth length, and we have therefore included these data. Thirteen trials with a total of 16,139 participants ([Belizan 1991](#); [Boggess 1997](#); [Crowther 1999](#); [Kumar 2009](#); [Levine 1997](#); [Lopez-Jaramillo 1989](#); [Purwar 1996](#); [Sanchez-Ramos 1994](#); [Sanchez-Ramos 1995](#); [Taherian 2002](#); [Villar 1990](#); [Villar 2006](#); [Wanchu 2001](#)) evaluated the effect of calcium supplementation on preterm birth before 37 weeks. Four trials, with 5669 participants ([Crowther 1999](#); [Kumar 2009](#); [Levine 1997](#); [Wanchu 2001](#)) evaluated the effect of calcium supplementation on preterm birth before 34 weeks. Six of the trials with 14,162 participants ([Crowther 1999](#); [Kumar 2009](#); [Levine 1997](#); [Lopez-Jaramillo 1989](#); [Villar 1990](#); [Villar 2006](#)) evaluated the effect of calcium supplementation on low birthweight (less than 2500 g). Seven trials ([Belizan 1991](#); [Crowther 1999](#); [Levine 1997](#); [Villar 1987](#); [Villar 1990](#); [Villar 2006](#); [Wanchu 2001](#)) evaluated side effects of calcium supplementation. For further details, see [Characteristics of included studies](#). No trials reported the effect of calcium supplementation on leg

cramps, backache, tetany, tremor, paraesthesia, osteopenia, osteoporosis, fracture in pregnant women, duration of breastfeeding or postpartum haemorrhage, and no trials reported on fetal or neonatal osteopenia, rickets and fracture.

Excluded studies

We excluded 20 trials from this review. The reasons for exclusion include: participants, interventions and methodology were not appropriate and there was insufficient information for inclusion. For more information, see [Characteristics of excluded studies](#). For more information about the studies which we have not yet assessed for inclusion, see [Characteristics of studies awaiting classification](#).

Risk of bias in included studies

The number of participants in trials ranged from 23 to 8325 per trial. The risk of bias in included studies varied. The overall missing data (lost to final analysis) were 4.01% (745 in 17842) ranging from (0% to 68.1%). Seven of the 23 trials contributing data had no missing data. Ten of the 23 trials had missing data less than 10%. Only one trial had a very high rate of missing data (68.1%). The largest trial had 0.16% missing data. The majority of included studies used methods of sequence generation and allocation concealment which we assessed as being at low risk of bias and overall, the included studies were assessed as low risk of bias for other domains of methodological quality. For an overview of review authors' judgments about each 'Risk of bias' item for individual included studies, see [Figure 1](#) and [Figure 2](#).

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

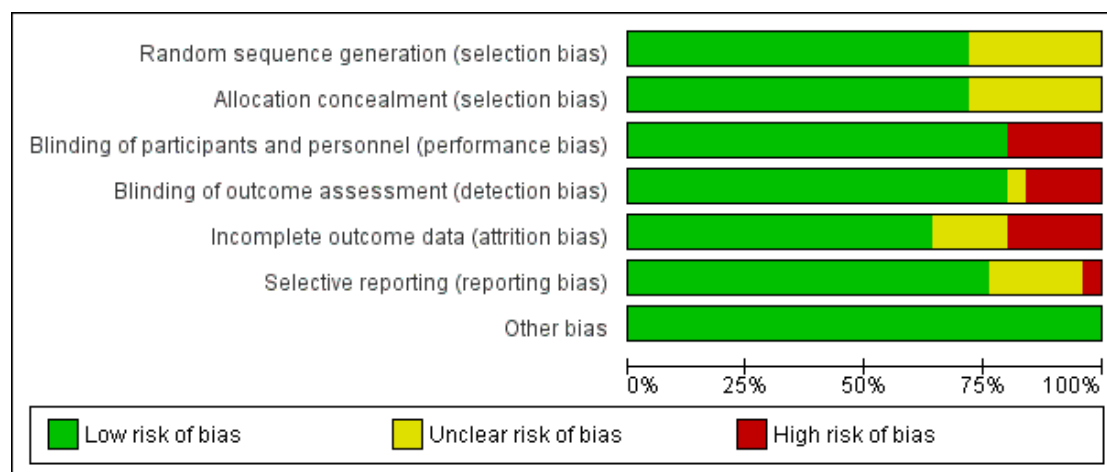


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Belizan 1983	?	?	+	+	+	+	+
Belizan 1991	+	+	+	+	+	+	+
Boggess 1997	+	+	+	+	?	+	+
Chan 2006	+	+	-	-	?	+	+
Crowther 1999	+	+	+	+	+	-	+
Ettinger 2009	?	?	+	+	?	+	+
Goldberg 2013	+	+	+	+	-	+	+
Herrera 2006	+	+	+	+	+	+	+
Jarjou 2006	+	+	+	+	-	+	+
Karandish 2003	?	?	+	+	-	+	+
Kumar 2009	+	+	+	+	+	+	+
Levine 1997	+	+	+	+	+	+	+
Lopez-Jaramillo 1989	+	+	+	+	?	?	+
Lopez-Jaramillo 1997	+	+	+	+	+	+	+
Niromanesh 2001	?	+	+	+	+	+	+
Purwar 1996	+	+	+	+	+	?	+
Raman 1978	?	?	-	-	-	?	+
Rogers 1999	?	?	-	?	+	?	+
Sanchez-Ramos 1994	+	+	+	+	+	+	+
Sanchez-Ramos 1995	+	+	+	+	+	+	+
Taherian 2002	+	?	-	-	+	+	+
Villar 1987	+	+	+	+	+	+	+
Villar 1990	+	+	+	+	+	+	+
Villar 2006	+	+	+	+	+	+	+
Wanchu 2001	?	?	-	-	-	?	+

Allocation

All studies included in this review were reported as being RCTs. Sample size calculation was clearly stated in only one trial (Crowther 1999). However, the two largest trials (Levine 1997; Villar 2006) had good methodological quality. Sequence generation was clearly described in 18 trials rated as 'low risk of bias' (Belizan 1991; Boggess 1997; Chan 2006; Crowther 1999; Goldberg 2013; Herrera 2006; Jarjou 2006; Kumar 2009; Levine 1997; Lopez-Jaramillo 1989; Lopez-Jaramillo 1997; Purwar 1996; Sanchez-Ramos 1994; Sanchez-Ramos 1995; Taherian 2002; Villar 1987; Villar 1990; Villar 2006). The remaining studies did not describe how the randomisation sequence was generated and were assessed as of unclear risk (Belizan 1983; Ettinger 2009; Karandish 2003; Niromanesh 2001; Raman 1978; Rogers 1999; Wanchu 2001).

Adequate allocation concealment was reported in 18 trials, and these were rated as 'low risk of bias' (Belizan 1991; Boggess 1997; Chan 2006; Crowther 1999; Goldberg 2013; Herrera 2006; Jarjou 2006; Kumar 2009; Levine 1997; Lopez-Jaramillo 1989; Lopez-Jaramillo 1997; Niromanesh 2001; Purwar 1996; Sanchez-Ramos 1994; Sanchez-Ramos 1995; Villar 1987; Villar 1990; Villar 2006). The remaining studies did not describe allocation concealment.

Blinding

Most of studies were considered to be of low risk of performance bias and detection bias. Double-blinding was reported in 20 studies (Belizan 1983; Belizan 1991; Boggess 1997; Crowther 1999; Ettinger 2009; Goldberg 2013; Herrera 2006; Jarjou 2006; Karandish 2003; Kumar 2009; Levine 1997; Lopez-Jaramillo 1989; Lopez-Jaramillo 1997; Niromanesh 2001; Purwar 1996; Sanchez-Ramos 1994; Sanchez-Ramos 1995; Villar 1987; Villar 1990; Villar 2006). One study (Chan 2006) was unable to blind because the groups consumed different food. The four trials using 'no treatment' as the control group were unable to blind the participants (Raman 1978; Rogers 1999; Taherian 2002; Wanchu 2001).

Incomplete outcome data

Most studies reported incomplete outcome data. Intention-to-treat (ITT) analyses was used in 11 trials assessed as of low or unclear risk of attrition bias (Belizan 1983; Belizan 1991; Crowther 1999; Kumar 2009; Lopez-Jaramillo 1989; Niromanesh 2001; Rogers 1999; Taherian 2002; Villar 1987; Villar 1990; Villar 2006). Goldberg 2013 also used ITT analysis, but the attrition rate was 20%; the trial was assessed as high risk of bias. Four additional trials did not use ITT analyses and were assessed

as high risk of bias for incomplete outcome data (Jarjou 2006; Karandish 2003; Raman 1978; Wanchu 2001). The remaining trials did not conduct ITT analyses but were assessed as unclear or low risk for attrition bias (Boggess 1997; Chan 2006; Herrera 2006; Lopez-Jaramillo 1997; Purwar 1996; Sanchez-Ramos 1994; Sanchez-Ramos 1995). The rate of losses to follow-up varied from 0% to 68.1%.

Selective reporting

We did not have the protocols for all the included studies; therefore we could not fully address selective reporting. Where trials specified their intended outcomes for analyses and then also presented relevant data for all of these outcomes, we assessed the trial as of low risk of bias.

Other potential sources of bias

None identified.

Effects of interventions

See: [Summary of findings for the main comparison](#) Calcium supplementation versus placebo or no treatment (maternal outcomes) for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: Calcium supplementation versus placebo or no treatment

Primary outcomes

Maternal outcomes

1. Preterm birth less than 37 weeks' gestation

Thirteen trials (Belizan 1991; Boggess 1997; Crowther 1999; Kumar 2009; Levine 1997; Lopez-Jaramillo 1989; Purwar 1996; Sanchez-Ramos 1994; Sanchez-Ramos 1995; Taherian 2002; Villar 1990; Villar 2006; Wanchu 2001) with data for 16,139 women. There were 8074 women who received calcium supplementation and 8065 women who received placebo or no treatment. Meta-analysis evaluating the effect of calcium supplementation versus placebo or no treatment on preterm birth before 37 weeks revealed that there was no statistically significant difference

between the two groups (average risk ratio (RR) 0.86, 95% confidence interval (CI) 0.70 to 1.05; random-effects model; [Analysis 1.1](#)). However, there was substantial heterogeneity between trials ($\text{Tau}^2 = 0.05$; $\text{Chi}^2 = 25.60$, $\text{df} = 11$ ($P = 0.007$); $I^2 = 57\%$). Therefore, we explored the source of heterogeneity by subgroup analyses stratified by total dose of calcium per day (less than 1000 mg/day or 1000 mg/day or more), starting time of calcium supplementation (before or after 20 weeks) and type of calcium (calcium carbonate, lactate and gluconate).

For total dose of calcium per day, there appeared to be a difference between subgroups (Test for subgroup differences: $\text{Chi}^2 = 6.93$, $\text{df} = 1$ ($P = 0.008$), $I^2 = 85.6\%$; [Analysis 1.2](#)). However, only one study was included in the low-dose subgroup ([Taherian 2002](#)), while 12 studies were in the high-dose subgroup, so this apparent difference between groups may have occurred by chance.

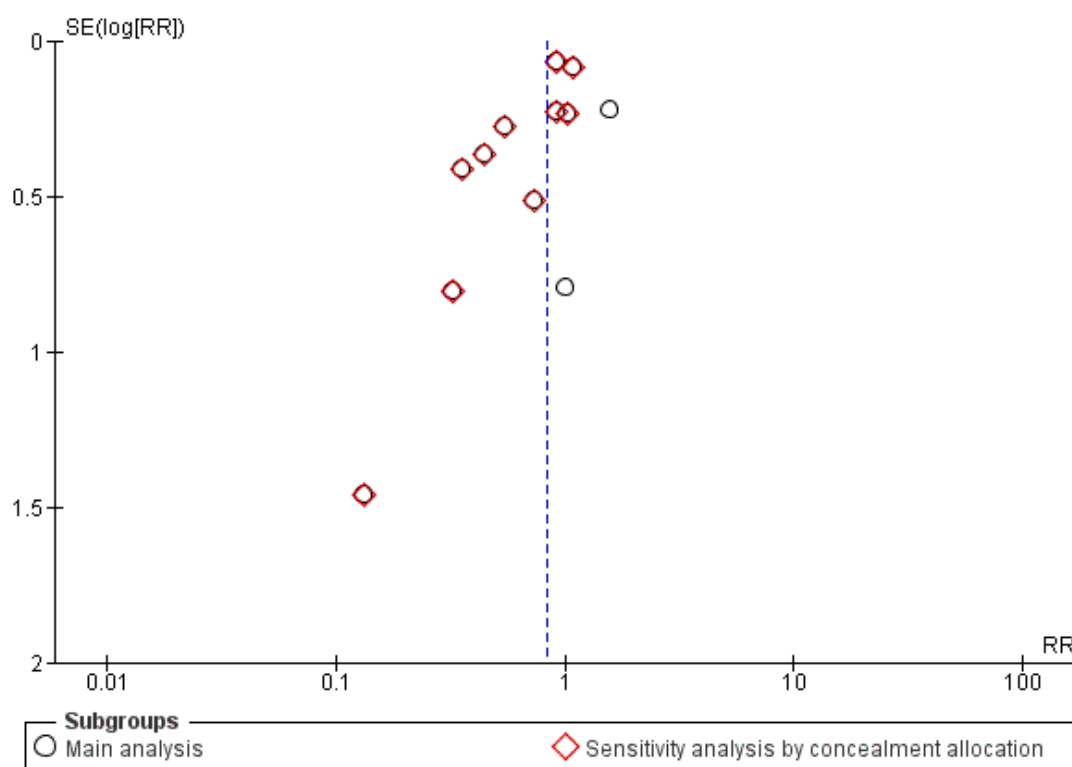
For the starting time of calcium supplementation, we found that there was no statistically significant differences between subgroups for women who started calcium before 20 weeks and for women who started calcium at 20 weeks or more ([Analysis 1.3](#)).

For type of calcium, there was no statistically significant difference between subgroups when women received calcium carbonate or

calcium gluconate; however only one trial gave calcium gluconate to 92 women and in this study there was no preterm birth before 37 weeks in either the treatment or placebo group ([Analysis 1.4](#)). We also conducted sensitivity analyses by removing two included trials ([Taherian 2002](#); [Wanchu 2001](#)) whose allocation of concealment was unclear. The results then favoured treatment with calcium supplementation (RR 0.80, 95% CI 0.65 to 0.99; 11 trials, 15,379 women; random-effects model; [Analysis 1.1](#)). There was significant heterogeneity for this outcome ($\text{Tau}^2 = 0.04$; $\text{Chi}^2 = 20.46$, $\text{df} = 9$ ($P = 0.02$); $I^2 = 56\%$).

To investigate possible publication bias we generated a funnel plot (see [Figure 3](#)). Visual examination of the funnel plot suggested there might be some asymmetry and the possibility of publication bias. However, substantial heterogeneity (as is found with this outcome), reporting bias and chance can each contribute to funnel plot asymmetry ([Sterne 2011](#)). Further, there were only 13 trials included in the analysis, and for outcomes with heterogeneity the minimum of recommendation of 10 trials may not be adequate ([Sterne 2011](#)). We therefore concluded that there was no strong evidence of publication bias for the outcome of preterm birth before 37 weeks.

Figure 3. Funnel plot of comparison: I Calcium supplementation versus placebo or no treatment (maternal outcomes), outcome: I.1 Preterm birth (a) Birth prior to 37 weeks.



Infant outcomes

1. Low birthweight (less than 2500 g)

There was no statistically significant protective effect of calcium supplementation on low birthweight (six trials, [Crowther 1999](#); [Kumar 2009](#); [Levine 1997](#); [Lopez-Jaramillo 1989](#); [Villar 1990](#); [Villar 2006](#), with 14,162 women); (RR 0.93, 95% CI 0.81 to 1.07; random-effects model). However, there was significant heterogeneity between trials ($\text{Tau}^2 = 0.01$; $\text{Chi}^2 = 10.61$, $\text{df} = 4$ ($P = 0.03$); $I^2 = 62\%$; [Analysis 2.1](#)). Women from these trials all received a high dose.

We planned to carry out subgroup analyses for starting time and for type of calcium supplementation. There was some evidence that the starting time of supplementation was associated with different treatment effects (Test for subgroup differences: $\text{Chi}^2 = 8.77$, $\text{df} = 1$ ($P = 0.003$), $I^2 = 88.6\%$). In two studies supplementation started early and there was no evidence of a significant difference between treatment and control groups (RR 0.98, 95% CI 0.94 to 1.03; three trials, 13,425 women), whereas the treatment appeared to have a significant effect in studies where supplementation started after 20 weeks' gestation (RR 0.41, 95% CI 0.23 to 0.73; three trials, 737 women). However, as a total of only six studies contributed estimable data to this subgroup analysis, these differences may have occurred by chance ([Analysis 2.2](#)). For type of calcium supplementation, most studies ([Crowther 1999](#); [Kumar 2009](#); [Levine 1997](#); [Villar 1990](#); [Villar 2006](#)) used calcium carbonate and one trial ([Lopez-Jaramillo 1989](#)) used calcium gluconate ([Analysis 2.3](#)).

We did not conduct sensitivity analyses because all included trials for this outcome were rated as 'low risk of bias' for allocation of concealment.

We did not investigate publication bias for this outcome because the number of included trials was insufficient (six trials).

Secondary outcomes

Maternal outcomes

1. Preterm birth less than 34 weeks' gestation

There was no statistically significant difference in birth prior to 34 weeks between calcium supplementation versus placebo or no treatment (four trials, [Crowther 1999](#); [Kumar 2009](#); [Levine 1997](#); [Wanchu 2001](#), 5669 women) (RR 1.04, 95% CI 0.80 to 1.36)

([Analysis 1.5](#)). We did not perform subgroup analysis for this outcome as there was no evidence of substantial heterogeneity ($I^2 = 0\%$).

We performed a sensitivity analyses and removed one included trial ([Wanchu 2001](#)) that had 'unclear' risk of bias for allocation concealment. The result did not change (RR 1.03, 95% CI 0.79 to 1.35, three trials, 5569 women) ([Analysis 1.6](#)).

2. Maternal weight gain

Three trials ([Lopez-Jaramillo 1989](#); [Lopez-Jaramillo 1997](#); [Villar 1987](#), 404 women) evaluated the effect of calcium supplementation on maternal weight gain. There was no statistically significant difference between treatment versus placebo or no treatment. We found no statistically significant difference between groups (mean difference (MD) -29.46 g per week, 95% CI -119.80 to 60.89 g per week; random-effects model) ([Analysis 1.7](#)). There was also substantial heterogeneity between trials ($\text{Tau}^2 = 5007.60$, $I^2 = 80\%$).

3. Maternal bone mineral density (BMD)

There was only one trial, involving 273 women ([Raman 1978](#)) that evaluated the effect of calcium supplementation and placebo on BMD. The author used radiographic density calculated and expressed in terms of aluminium equivalents as defined by Williams and Mason ([Williams 1962](#)).

We have presented the data for this outcome separately for treatment arms receiving different doses of supplementation.

In calcium 300 mg:

- first phalanx: there was no statistically significant difference between treatment versus placebo or no treatment (62 women, MD -0.07 g/cm², 95% CI -0.29 to 0.15 g/cm² ([Analysis 1.8](#)));
- second metacarpal: there was no statistically significant difference between treatment versus placebo or no treatment (62 women, MD 0.19 g/cm², 95% CI -0.02 to 0.40 g/cm² ([Analysis 1.9](#)));
- fourth metacarpal: there was no statistically significant difference between treatment versus placebo or no treatment (62 women, MD 0.06 g/cm², 95% CI -0.17 to 0.29 g/cm² ([Analysis 1.10](#))).

In calcium 600 mg:

- first phalanx: there was no statistically significant difference between treatment versus placebo or no treatment (63 women, MD 0.09 g/cm², 95% CI -0.10 to 0.28 g/cm² ([Analysis 1.11](#)));

- second metacarpal: there was no statistically significant difference between treatment versus placebo or no treatment (63 women, MD 0.14 g/cm², 95% CI -0.11 to 0.39 g/cm² ([Analysis 1.12](#)));
- fourth metacarpal: there was no statistically significant difference between treatment versus placebo or no treatment (63 women, MD 0.07 g/cm², 95% CI -0.13 to 0.27 g/cm² ([Analysis 1.13](#))).

4. Maternal death

Two trials involving 8974 women ([Goldberg 2013](#); [Villar 2006](#)) reported this outcome. Although there appeared to be fewer deaths in the group receiving calcium supplements compared with controls (two versus seven), the difference between groups was not statistically significant (RR 0.29, 95% CI 0.06 to 1.38; [Analysis 1.14](#)).

5. Maternal admission to intensive care unit

Only one trial with 8312 women reported on this outcome ([Villar 2006](#)). There was no statistically significant difference between treatment and control groups (RR 0.84, 95% CI 0.66 to 1.07) ([Analysis 1.15](#)).

6. Mode of birth - vaginal birth, Instrumental vaginal birth, caesarean section (non-prespecified outcome)

- Vaginal birth: eight trials involving 6916 women ([Belizan 1991](#); [Crowther 1999](#); [Levine 1997](#); [Purwar 1996](#); [Rogers 1999](#); [Sanchez-Ramos 1995](#); [Villar 1990](#); [Wanchu 2001](#)) reported on this outcome. There was no statistically significant difference between treatment and control groups (RR 1.01, 95% CI 0.99 to 1.03) ([Analysis 1.16](#)).
- Instrumental birth: two trials involving 675 women ([Crowther 1999](#); [Rogers 1999](#)) reported on this outcome. There was no statistically significant difference between treatment and control groups (RR 0.89, 95% CI 0.66 to 1.20) ([Analysis 1.17](#)).
- Caesarean section: nine trials involving 7440 women ([Belizan 1991](#); [Crowther 1999](#); [Kumar 2009](#); [Levine 1997](#); [Purwar 1996](#); [Rogers 1999](#); [Sanchez-Ramos 1995](#); [Villar 1990](#); [Wanchu 2001](#)) reported on this outcome. There was no statistically significant difference between treatment and control groups (RR 0.99, 95% CI 0.89 to 1.10) ([Analysis 1.18](#)).

7. Postpartum haemorrhage (non-prespecified outcome)

Data were not available for this outcome.

Data were not available for the following maternal secondary outcomes: leg cramps; backache; tetany (muscle spasm and twitching); incidence of fracture; duration of breastfeeding; tremor; paraesthesia.

Fetal and neonatal outcomes

1. Perinatal mortality

Eight trials (15,785 women) reported perinatal mortality ([Belizan 1991](#); [Goldberg 2013](#); [Levine 1997](#); [Lopez-Jaramillo 1997](#); [Sanchez-Ramos 1994](#); [Sanchez-Ramos 1995](#); [Taherian 2002](#); [Villar 2006](#)). There was no statistically significant difference between the groups (RR 0.87, 95% CI 0.72 to 1.06) ([Analysis 2.5](#)).

2. Stillbirth or fetal death

Six trials ([Crowther 1999](#); [Goldberg 2013](#); [Kumar 2009](#); [Levine 1997](#); [Taherian 2002](#); [Villar 2006](#)) involving 15,269 women reported stillbirth or fetal death separately. There was no statistically significant difference between the groups (RR 0.91, 95% CI 0.72 to 1.14) ([Analysis 2.6](#)).

3. Neonatal death

Data were not available for this outcome.

4. Admission to neonatal intensive care unit

Admission to neonatal intensive care unit was reported in four trials involving 14,062 women ([Belizan 1991](#); [Levine 1997](#); [Sanchez-Ramos 1994](#); [Villar 2006](#)). There was no statistically significant difference between the groups (RR 1.05, 95% CI 0.94 to 1.18; I² = 0%) ([Analysis 2.7](#)).

5. Birthweight

Mean birthweight (g) was reported in 21 trials involving 9202 women ([Belizan 1983](#); [Belizan 1991](#); [Bogges 1997](#); [Chan 2006](#); [Crowther 1999](#); [Goldberg 2013](#); [Karandish 2003](#); [Kumar 2009](#); [Levine 1997](#); [Lopez-Jaramillo 1989](#); [Lopez-Jaramillo 1997](#); [Niromanesh 2001](#); [Purwar 1996](#); [Raman 1978](#); [Rogers 1999](#); [Sanchez-Ramos 1994](#); [Sanchez-Ramos 1995](#); [Taherian 2002](#); [Villar 1987](#); [Villar 1990](#); [Wanchu 2001](#)). (In the trials by [Belizan 1983](#) and [Raman 1978](#) data were reported separately for women receiving different doses of calcium; in the meta-analysis we have therefore included findings for different doses separately as there

was some heterogeneity between the different treatment arms; in both cases we divided the control group between the two entries to avoid double counting.) There was a statistically significant difference in birthweight between the groups (MD 56.40, 95% CI 13.55 to 99.25); $\text{Tau}^2 = 5668.70$, $I^2 = 74\%$; random-effects model) (Analysis 2.4) with the women in the calcium supplementation group on average having heavier babies than those in the control group.

6. Birth length

Birth length was reported in seven trials (6389 women) (Belizan 1983; Belizan 1991; Goldberg 2013; Karandish 2003; Levine 1997; Raman 1978; Villar 1990). There was no statistically significant difference between the groups (MD -0.09, 95% CI -0.25 to 0.06) (Analysis 2.8).

7. Head circumference

Three trials involving 460 women reported head circumference (Belizan 1983; Goldberg 2013; Karandish 2003) (again data for the two treatment arms of the Belizan 1983 trial were entered separately with the control group shared between entries). There was no statistically significant difference between the groups (MD -0.09, 95% CI -0.36 to 0.18) (Analysis 2.9).

8. Intrauterine growth restriction

Intrauterine growth restriction was reported in six trials involving 1701 women (Kumar 2009; Purwar 1996; Sanchez-Ramos 1994; Sanchez-Ramos 1995; Taherian 2002; Villar 1990). There was no statistically significant difference between the groups (RR 0.83, 95% CI 0.61 to 1.13) (Analysis 2.10).

9. Neonatal BMD

We presented the data for this outcome separately as subgroups (with subtotals only) due to the different definition of this outcome as defined by authors (Analysis 2.11):

- total body: there was no statistically significant difference between treatment versus placebo or no treatment in two trials, 300 women (Jarjou 2006; Levine 1997; MD 0.00 g/cm², 95% CI 0.00 to 0.01 g/cm²; $I^2 = 0\%$);
- midshaft radius: there was no statistically significant difference between treatment versus placebo or no treatment in one trial involving 122 women (Jarjou 2006; MD 0.00 g/cm², 95% CI -0.01 to 0.01 g/cm²);
- lumbar spine 1 to 4: there was no statistically significant difference between treatment versus placebo or no treatment in

one trial involving 256 women (Levine 1997; MD 0.01 g/cm², 95% CI 0.00 to 0.02 g/cm²).

We have excluded the data from the Raman 1978 trial from our meta-analysis because they were skewed but they have been presented separately in an additional table (see Table 1).

Data were not available for the following secondary fetal and neonatal outcomes: osteopenia; rickets; fracture.

Adverse outcomes, compliance and maternal satisfaction

1. Side effects of calcium supplementation

Four trials reported side effects of calcium supplementation (Belizan 1991; Villar 1987; Villar 2006; Wanchu 2001). We have presented the data for this outcome separately as subgroups (with subtotals only) due to the different definitions of this outcome in the trials (Analysis 3.1).

- Maternal cholestatic jaundice: there was no statistically significant difference between the groups in one trial involving 100 women (Wanchu 2001) (RR 3.00, 95% CI 0.13 to 71.92).
- Gastrointestinal symptoms consisting of nausea, heartburn and diarrhoea: there was no statistically significant difference between the groups in one trial involving 52 women (Villar 1987) (RR 2.16, 95% CI 0.43 to 10.78).
- Gall stones: there was no statistically significant difference between the groups in one trial involving 518 women (Belizan 1991) (RR 1.35, 95% CI 0.48 to 3.85).
- Headache, vomiting, backache, swelling, vaginal and urinary complaints, dyspepsia, abdominal pain: there was no statistically significant difference between the groups in one trial involving 8312 women (Villar 2006) (RR 1.02, 95% CI 0.93 to 1.12).

2. Urinary stones

Three trials involving 13,419 women reported this outcome (Belizan 1991; Levine 1997; Villar 2006). There was no statistically significant difference between the groups (RR 1.11, 95% CI 0.48 to 2.54; $I^2 = 39\%$) (Analysis 3.2).

3. Urinary tract infection

Three trials involving 1743 women reported this outcome (Belizan 1991; Crowther 1999; Villar 1990). There was no statistically significant difference between the groups (RR 0.95, 95% CI 0.69 to 1.30; $I^2 = 0\%$) (Analysis 3.3).

5. Renal colic

This outcome was reported in one trial with 8312 women (Villar 2006). There was no evidence of a statistically significant difference between groups (RR 1.67, 95% CI 0.40 to 6.99) (Analysis 3.4).

5. Impaired renal function

There was no statistically significant difference between the groups for this outcome in one trial, involving 4589 women (Levine 1997) (RR 0.91, 95% CI 0.51 to 1.64) (Analysis 3.8) (Analysis 3.5).

6. Maternal anaemia

One trials, involving 1098 women, reported this outcome (Belizan 1991). There was no statistically significant difference between the groups (RR 1.04, 95% CI 0.9 to 1.22) (Analysis 3.6).

7. Compliance

Data were not available for this outcome.

8. Satisfaction

Data were not available for this outcome.

DISCUSSION

Summary of main results

Calcium supplementation did not reduce preterm birth. Dosage, prescription timing and the type of calcium supplementation did not effect this outcome. Calcium supplementation did not decrease the rate of low birthweight. Timing of supplementation and the type of calcium supplementation did not show any clear protective effect for low birthweight. No trial reported the effect of low-dose calcium supplementation (less than 1000 mg) on low birthweight babies. There was no evidence that calcium supplementation had any effect on maternal weight gain during pregnancy. There was no evidence to support the benefit of calcium supplementation in increasing bone mineral density in pregnant women but in infants, there was a statistically significant difference between treatment and placebo or no treatment in total body and tibial bone mineral density. While there was a statistically significant increase in birthweight in the calcium supplementation group, there was also high heterogeneity among the studies, so the results for this outcome should be interpreted with caution. Additionally, the 56 g increase in birthweight might not be clinically important. There was no evidence that calcium supplementation reduced the rate of intrauterine growth restriction, perinatal mortality, stillbirth or fetal death rate. Calcium supplementa-

tion also did not increase birth length or fetal head circumference. We found no evidence to show that calcium supplementation was associated with side effects such as postpartum haemorrhage, cholestatic jaundice, gall stones, gastrointestinal symptoms, headache, urinary stones, urinary tract infection or impaired renal function.

Overall completeness and applicability of evidence

Missing data amounted to 4.01% overall (745 in 17,842). One small trial showed a marked loss of follow-up (68.1%, Raman 1978). The loss to follow-up rates in most trials were less than 20%. Most trials prespecified outcomes in included studies especially the primary outcomes, but no data were reported for some of our secondary outcomes. As we mentioned above, the primary objectives of most of the included studies were incidence of pregnancy-induced hypertension or changes in blood pressure, which were not relevant to this review. However, these studies also had other outcomes relevant to this review, e.g. preterm birth, maternal weight gain, gestational age, birthweight, birth length and therefore, we have included them.

The largest trial in this review (Villar 2006) recruited pregnant women from a population who received less than 600 mg of dietary calcium per day. The other two big trials (Belizan 1991; Levine 1997) did not limit daily calcium intake. In addition, there were variations between trials in terms of duration of supplementation. The subgroup analysis to assess the effect on preterm delivery before 37 weeks of calcium supplementation before versus after 20 weeks' gestation revealed no protective effect on either group. There were too few studies to assess other types of calcium prescribed or other outcomes of interest such as preterm delivery before 34 weeks, maternal bone mineral density, and major fetal outcomes. This may be evidence that routine calcium supplementation in pregnant women for preventing preterm birth and low birthweight is not warranted.

The largest trial in this review (Villar 2006) recruited pregnant women from a population who received less than 600 mg of dietary calcium per day. The other two big trials (Belizan 1991; Levine 1997) did not limit daily calcium intake. In addition, there were variations between trials in terms of duration of supplementation. The main analysis to assess the effect on preterm delivery before 37 and 34 weeks did not show significant benefit, but in a sensitivity analysis of 11 low risk of bias trials (Belizan 1991; Boggess 1997; Crowther 1999; Kumar 2009; Levine 1997; Lopez-Jaramillo 1989; Purwar 1996; Sanchez-Ramos 1994; Sanchez-Ramos 1995; Villar 1990; Villar 2006), there was a statistically significant benefit of calcium supplementation in reducing preterm delivery less than 37 weeks. Type of calcium supplementation and timing for prescribing did not make any differences.

Hofmeyr 2014 found a reduction in preterm birth for women receiving high-dose calcium supplementation (11 trials, 15,275

women; risk ratio (RR) 0.76, 95% confidence interval (CI) 0.60 to 0.97; $I^2 = 60\%$). [Hofmeyr 2014](#) also found a reduction in the risk of developing pre-eclampsia for women receiving supplementation (13 trials, 15,730 women; RR 0.45, 95% CI 0.31 to 0.65; $I^2 = 70\%$). There were eight trials in common for the preterm outcome for this and the Hofmeyr review. However, results for the preterm birth prior to 37 weeks outcome in this systematic review did not reach statistical significance until two trials were removed during sensitivity analysis (see [Analysis 1.1](#)). Inclusion criteria between the reviews differed, and therefore the results were also different.

Quality of the evidence

Most of the studies (17 of the 25 trials) were at low risk of bias for both sequence generation and allocation concealment, see [Figure 1](#) and [Figure 2](#). Seven trials did not describe the methods of sequence generation or allocation concealment clearly. Three outcomes were chosen for assessment with GRADE software for quality: low birthweight (less than 2500 g), preterm birth less than 37 weeks and preterm birth less than 34 weeks. Evidence for each outcome was considered to be of moderate quality.

Potential biases in the review process

We followed methods set out in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)) to try to reduce bias in the review process.

Agreements and disagreements with other studies or reviews

A Cochrane review by [Hofmeyr 2014](#) entitled '*Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems*' showed that routine calcium supplementation during pregnancy reduced the risk of pre-eclampsia and preterm birth. As discussed above, some of our results differ from [Hofmeyr 2014](#) due to differing inclusion criteria.

AUTHORS' CONCLUSIONS

Implications for practice

This review found that calcium supplementation did not reduce preterm birth less than 37 weeks. There is not enough evidence to assess dosage, timing and type of calcium supplementation on pregnancy outcomes other than pregnancy-induced hypertension. The review by [Hofmeyr 2014](#) shows a significant protective effect of calcium supplementation on pre-eclampsia/eclampsia, and reduced preterm birth but our review reveals no additional benefits of calcium supplementation. The discrepancy result might be due to inadequate sample size. Therefore, calcium supplementation during pregnancy would be primarily considered to prevent pre-eclampsia.

Implications for research

Large multicentre trials to detect the benefit of calcium supplementation on preterm birth as the primary outcome are needed to provide more solid evidence.

In addition, the results from this review found that there are a few short-term additional benefits of calcium supplementation (other than pre-eclampsia prevention) other than slight increases fetal birthweight and neonatal bone mineral density. There are limited data to assess its long-term benefits such as osteoporosis in later life. Further research might be needed to provide evidence regarding long-term benefits.

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Buppasiri P, Lumbiganon P, Thinkhamrop J, Ngamjarus C, Laopaiboon M. Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes. *Cochrane Database of Systematic Reviews* 2011, Issue 10. [DOI: 10.1002/14651858.CD007079.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Belizan 1983

Methods	Type of study: simple randomisation into 3 groups. Method of treatment allocation: not stated. Placebo: yes, starch tablets. Sample size calculation: not stated. Intention-to-treat analyses: yes. Losses to follow-up: 0%.	
Participants	Location: outpatient clinic of Guatemala Social Security Hospital. Time frame: not stated. Eligible criteria: age 20 to 35 years, single fetus, without evidence of previous pathology and certain date, not receiving any medical treatment during recruitment. Total recruited: 36 pregnant women. Treatment group 1, n = 11, treatment group 2, n = 11, placebo group, n = 14	
Interventions	● Treatment Group 1 : 1 g calcium/d. ● Treatment Group 2 : 2 g calcium/d. ● Compared with placebo tablets. Started treatment at 15 weeks until delivery.	
Outcomes	1. BP. 2. Parathyroid hormone. 3. Calcium and magnesium level. 4. Phosphorus level. 5. Pregnancy outcomes; birthweight, birth length, head circumference.	
Notes	The authors did not mention how many tablets were provided in calcium 1 g, 2 g and placebo group Missing data = 0%. For data in Analysis 2.4 and Analysis 2.9 the placebo n was halved to enable inclusion of data for treatment groups 1 and 2	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "After the patients volunteers to participate the trial. Simple randomisation were used to devise patient into 3 groups, receive 1, 2 g calcium comparing with placebo." Comment: method of random sequence generation was not clearly described

Belizan 1983 (Continued)

Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment was not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients were unaware of group status. Study drug and placebo were the same size and weight and had the same organoleptic characteristics
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only 3 obstetrics and gynaecology residents were in charge of measuring BP, after standardisation with double auricular stethoscope
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all enrolled participants were analysed. Missing data = 0%.
Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

Belizan 1991

Methods	Type of study: multicentre, double-blind, randomised controlled trial. Method of treatment allocation: randomisation was conducted at each hospital by a random-generator program. A complete set of numbered, sealed, opaque envelopes containing the randomisation codes was sent to each of 3 hospitals. Placebo: yes, starch tablets. Sample size calculation: not stated. Intention-to-treat analyses: yes. Losses to follow-up: 2.3%. 27 women were lost to follow-up after randomisation (14 in the calcium group, 13 in the placebo group) but before they started treatment, and therefore were not included in the followed up analyses. Follow-up was incomplete for 52 women in the calcium group and 46 in placebo group because of change of hospital, physician or residence
Participants	Location: the women enrolled from 3 affiliated hospitals of Centro Rosario de Estudios Perinatales, Rosario, Argentina (2 were public hospitals, the another was a private hospital). Time frame: January 1987 to September 1989. Eligible criteria: GA < 20 weeks and confirmed by ultrasound, nulliparous, singleton pregnancy, BP < 140/90 mmHg. No evidence of present or past disease from clinical examination or laboratory tests, not taking any medications and had normal glucose tolerance test. Exclusion criteria: gestational date estimated from LMP and ultrasonography different by more than 10 days. Total recruited: 1194 pregnant women; treatment group, n = 593, control group, n = 601. A total of 579 women in the calcium group and 588 in the placebo group were

	included in final analyses	
Interventions	2 g calcium/d (4 tablets/day; each calcium tablet contained 500 mg calcium carbonate and granulated starch). Compared with placebo tablet. Started treatment at 20 weeks.	
Outcomes	1. BP. 2. Serum total calcium. 3. Serum magnesium. 4. Urinary calcium excretion. 5. Serum phosphate. 6. Serum uric acid. 7. Pregnancy outcomes; birthweight, birth length, preterm birth, premature rupture of membrane, diabetic mellitus, third trimester bleeding, numbers of hospital admission, perinatal death. 8. Rate of urinary tract infection. 9. Rate of maternal anaemia.	
Notes	Treatment group, n = 593, control group, n = 601. For final analysis, treatment group, n = 579, 588 in placebo group but for other pregnancy outcomes other than pregnancy hypertension, n = 544 in calcium group and n = 554 in control group Missing data 27 in 1194 = 2.3%.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "They were randomised at each hospital by a random-generator program."
Allocation concealment (selection bias)	Low risk	Quote: "A complete set of numbered, sealed, opaque envelopes containing the randomisation codes was sent to each of three hospitals."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The calcium tablets were specially prepared by a local pharmaceutical company; the placebo tablets contained lactose and granules starch and were identical to the calcium tablets with respect to weight, size, flavour and colour. The nurses and physicians responsible for prenatal care were all unaware of the women's treatment status
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The nurses and physicians responsible for prenatal care were all unaware of the women's treatment status and were also responsible for distribution the bottle of medications, taking BP and collection of

Belizan 1991 (Continued)

		blood and urine samples at every visit
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Follow-up was incomplete 52 in treatment group and 46 in placebo group because of change of hospital, physician, or residence. Nonetheless, all were included in analyses up to time when they were lost to follow-up. For the subgroup with incomplete follow-up, information about delivery was available for 17 in calcium group and 12 in placebo group." Missing data 27 in 1194 = 2.3%.
Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

Bogges 1997

Methods	Type of study: double-blind randomised controlled trial. Method of treatment allocation: a computer-generated random number table was used. Using a randomisation schedule in a block of 10. All containers and tablets were prepared and dispensed by the University Drug Pharmacy. Placebo: yes, starch tablets. Sample size calculation: not stated. Intention-to-treat analyses: no (23 women were randomised and 18 of them completed study). Of the 5 who did not complete the study, 3 developed preterm labour and 1 was non compliance, and 1 self-discontinued study medication due to side effects. Losses to follow-up: 5 in 23 = 21.7%.	
Participants	Location: University of Washington Medical Center Women's Clinic. Time frame: not stated. Eligible criteria: age 18 to 35 years who received antenatal care. Exclusion criteria: BP > 140/90 mmHg at 24 weeks, smoking or used illicit drugs, multiple gestation, had history of cardiovascular, renal, or endocrine disorder, hypertension prior to pregnancy, or calcium supplementation. Total recruited: 23 pregnant women; calcium group, n = 12, placebo group, n = 11	
Interventions	1.5 g/d of calcium carbonate. Compared with placebo tablets. Started treatment at 28 to 31 weeks	
Outcomes	Hemodynamic function measurement.	
Notes	1. GA was reported as median and range. We changed them into mean and SD	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Quote: "The study patients were assigned in a double-blind fashion to receive orally either 1.5 element calcium as calcium carbonate or placebo daily, using a randomisation schedule in blocks of ten developed by a computer-generated random number table."
Allocation concealment (selection bias)	Low risk	Quote: "All containers and tablets were prepared and dispensed by the University Drug Pharmacy."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment versus placebo. Quote: "Placebo tablets were same size, weight, colour, and organoleptic characteristics." All participants were blinded to intervention. All containers and tablets were prepared and dispensed by the University Drug Pharmacy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All containers and tablets were prepared and dispensed by the University Drug Pharmacy. The investigators were blinded to outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Twenty-three women were randomised and 18 of them completed study. Of the five who failed to complete the study; three developed preterm labour (all placebo), one was noncompliance (placebo), one discontinued due to side effects (calcium)." Missing data = 5 in 23 = 21.7%; relevant data such as preterm birth were added back into the analysis
Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

Methods	Type of study: computer-generated randomisation. Method of treatment allocation: the pregnant women were randomly assigned to 1 of 3 groups: control, orange juice fortified with calcium, and dairy. Computer-generated randomisation was kept in envelopes. Placebo: no. Sample size calculation: not stated. Intention-to-treat analyses: no. Losses to follow-up at delivery 8.3% : in control group, missing data at delivery = 0, missed 6 months visit, n = 3 and umbilical cord not collected, n = 2. In orange juice plus calcium missing data = 3, failed to meet required 4 servings, n = 12, misses 6 month visit, n = 3, and mothers blood was not collected, n = 3 and umbilical blood was not collected, n = 3. In dairy group, missing data at delivery = 3, missed at 6-month visit, n = 2, mother's blood was not collected, n = 3, and umbilical blood was not collected, n = 5
Participants	Location: University of Utah Teen Mother and Child Program. Time frame: not stated. Eligible criteria: healthy adolescent (15 to 17 years old) pregnant women. GA < 20 weeks by last normal menstrual period. Exclusion criteria: hypertension, diabetes, renal or liver diseases, used alcohol, tobacco or medications that would effect Ca metabolism during pregnancy. Total recruited: 72 healthy pregnant adolescents.
Interventions	There were 3 groups. Group 1; control (consumed usual diet) n = 23. Group 2; orange juice fortified with calcium consumed at least 4 servings of orange juice plus calcium (more than 1200 mg Ca) n = 24. Group 3; dairy (consumed at least 4 servings of dairy product (Ca more than 1200 mg) e.g., milk, yogurt, cheese, n = 25. Started treatment at 20 weeks
Outcomes	1. Maternal weight gain, BP. 2. Newborn birthweight, lean and fat mass of infant, total body calcium.
Notes	Missing data at delivery 6 in 72 = 8.3%.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Pregnant mothers were randomly assigned to one of three groups; control, orange juice fortified with calcium, and dairy. Computer-generated randomisation was kept in sealed envelopes."
Allocation concealment (selection bias)	Low risk	Quote: "Computer-generated randomisation was kept in sealed envelopes."
Blinding of participants and personnel (performance bias)	High risk	Quote: "The control group consumed their usual diet while the orange juice plus cal-

All outcomes		cium group were counselled to consume at least four servings of orange juice plus calcium (more than 1200 mg Ca) so that their Ca intake would be similar to the dairy group. The dairy group was counselled to consume at least four servings of dairy products (more than 1200 mg Ca) daily. Dairy products consisted of milk, yogurt, and cheese.” Comment: it was impossible to blind because of the different kinds of food
Blinding of outcome assessment (detection bias) All outcomes	High risk	Could not blind participants and investigators due to different intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: the authors displayed a flow chart of participants. Missing data in control group = 13%, in orange juice plus calcium = 12.5 %, in dairy product 8%. Missing data at delivery 6 in 72 = 8.3%
Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

Crowther 1999

Methods	Type of study: placebo-controlled double-blind trial. Method of treatment allocation: the randomisation schedule was prepared by the drug company with stratification made by centre using variable blocks. Placebo: yes, starch tablets. Sample size calculation: a study of 948 women was estimated to have an 80% probability of detecting differences in the rate of preterm birth at $P = 0.05$ and an 88% power to detect a 50% difference with the rate of PIH with the same significance level. Intention-to-treat analyses: yes. Pre-calculation samples needed 948 women to be recruited in trial but because of shortage of funds, but only 456 pregnant women were recruited. Losses to follow-up: 0%.
Participants	Location: 5 Australian Medical Centres. Time frame: August 1992 to December 1996. Eligible criteria: nulliparous, singleton pregnancy, at less than 24 weeks, with normal BP at trial entry ($< 140/90$ mmHg) and expected to birth at 5 collaborating centres were expected for trial but recruitment to the trial was stopped by the steering group without knowledge of study outcomes after 456 women were randomised when the limited financial resources available for the trial were exhausted. Exclusion criteria: used of antihypertensive or medical disorder where calcium supplementation was contraindicated such as renal failure, hyperparathyroidism or renal cal-

	culi. Total recruitments: 948 pregnant women planned to be recruited. Data were analysed when pregnancy outcome data were available for all 456 women recruited. Of 456, 227 were assigned to calcium group, 229 were in placebo group	
Interventions	Women were asked to take 3 tablets daily orally, equivalent 1.8 g calcium or placebo (calcium carbonate, 600 mg of elemental calcium per tablet). Started treatment at 20 weeks until delivery. Compared with 3 tablets of placebo tablets	
Outcomes	1. Incidence of PIH. 2. Pregnancy outcomes; preterm birth, premature rupture of membrane, birthweight	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation schedule was prepared by the drug company with stratification made by centre using variable blocks."
Allocation concealment (selection bias)	Low risk	Quote: "A study number was given by the central randomisation office. This corresponded to a sealed treatment pack held at the collaboration centre and were provided by Lederle Laboratories."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Women who gave consent were enrolled into the trial by telephoning the central randomization number in the Maternal Perinatal Clinic Trial Unit . The randomization schedule was prepared by the drug company with stratification made by center using variable blocks." All women and staff were blind to group assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Women received antenatal care and postnatal care from attending obstetrics care. Data were collected from case notes by research assistants and checked by senior obstetrician, all blinded to treatment allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "948 women were expected for trial but recruitment to the trial was stopped by the steering group without knowledge of study outcomes after 456 women were

		randomised when the limitation financial resource available for the trial were exhausted. Data were performing when pregnancy outcome data were available for all 456 women recruited. Of 456: 227 were assigned to calcium group, 229 were placebo group.” Comment: the number of participants in treatment and control groups was equal Missing data = 0%.
Selective reporting (reporting bias)	High risk	Trial stopped before enrolment complete due to a shortage of research funds
Other bias	Low risk	None identified.

Ettinger 2009

Methods	Type of study: Double-blind, randomised, placebo-controlled trial Method of treatment allocation: not stated Placebo: yes Intention-to-treat basis: yes
Participants	Location: Mexican Social Security Institute, Mexico city, Mexico Time frame: 2001-2003 670 women were randomised in the first trimester of pregnancy. 334 to the treatment group, and 336 to the placebo group
Interventions	1200 mg calcium daily (two 600-mg calcium carbonate tablets) versus placebo
Outcomes	Maternal blood lead levels at first, second, and third trimester
Notes	We have not included outcome data from this study as the trial specifically focused on the effects of calcium supplementation on blood lead levels. The study does not address any of the review's primary or secondary outcomes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women were randomly assigned to received 1200 mg calcium (2 tabs of 600 mg calcium carbonate tablets) or placebo.

Ettinger 2009 (Continued)

		Study described as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo-controlled trial. Study described as double-blind.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	670 randomised. 565 women completed follow-up. 557 included in the analysis (83%). Lost to follow-up in placebo 18%, calcium group 14%
Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

Goldberg 2013

Methods	Type of study: double-blind, randomised, parallel, placebo-controlled trial. Method of treatment allocation: stratified by clinic to receive calcium supplementation or placebo. The assignment within each stratum was by random permuted block of 4 in each week each clinic. The allocation sequence was generated by using random-number tables. The code was held by a member of the trial team who was not directly involve in data collection and had no contact with participant Placebo: yes, starch tablets. Sample size calculation: at 5% significance and 80% power, a sample size needed 260 participants per group Loss to follow-up: 330 randomised to intervention and 332 to the control group. Data for 260 women in the intervention group and 265 in the control group at delivery. Attrition accounted for in study flowchart with numbers given for maternal (2), fetal (10), neonatal or infant death (25); exclusion after randomisation for incorrect GA (70) or multiple pregnancy (11) missing data for BP at 36 weeks' gestation (1) and women moving away or withdrawal (18). ITT and per protocol analyses undertaken. 3 women unaccounted for in flowchart Jarjou 2006 presents data for a subset of the women in reported in Goldberg 2013, for the outcome of neonatal bone density.
Participants	Location: 3 antenatal clinics, covering cluster of villages in different geographic regions in West Kiangin Gambia. Time frame: May 1995 - March 2000. Eligible criteria: healthy pregnant women with no medical history affecting calcium metabolism presenting for prenatal care at 1 of 3 outpatient clinics. Singleton only, gestation 18-22 weeks Exclusion criteria: any complications of pregnancy. Total recruitments: 662 pregnant women were recruited, 330 in treatment group, 332 in placebo group. Data for 525, with loss to groups comparable
Interventions	1500 mg calcium (3 chewable calcium carbonate tablets, each consist of 500 mg elemental calcium) versus 3 chewable placebo in similar shape, colour, and taste, from 20 weeks'

	gestation until delivery	
Outcomes	BP at 36 weeks' gestation. Maternal BP in first year postpartum. Infant growth measures collected at 2, 13 and 52 weeks Breast milk calcium concentration, neonatal bone mineral density at age < 1 year.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Double-blind, randomised, parallel, placebo-controlled trial. The assignment within each stratum was by random permuted block of 4 in each week at each clinic. The allocation sequence was generated by using random-number tables
Allocation concealment (selection bias)	Low risk	The allocation sequence was generated by using random-number tables
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment group and placebo group received identical tablets
Blinding of outcome assessment (detection bias) All outcomes	Low risk	BP, anthropometric measurements were measured by trained field staff using a standard protocol
Incomplete outcome data (attrition bias) All outcomes	High risk	330 randomised to intervention and 332 to the control group. Data for 260 women in the intervention group and 265 in the control group at delivery. Attrition in both arms approximately 20%. Authors accounted for women lost in flowchart and conducted ITT analysis where possible. For infant outcomes, the denominator varies. Many infants without data for birth measurements because their mothers spent the traditional 8-day confinement period away from their village
Selective reporting (reporting bias)	Low risk	Prespecified outcomes are reported.
Other bias	Low risk	None detected.

Herrera 2006

Methods	Randomised controlled trial. Study described as placebo-controlled and double-blind
Participants	Location: 3 clinical settings in Santander de Quilichao and Cali, Columbia Healthy pregnant adolescent women < 19 yrs, between 17 and 19 weeks pregnant. Primigravidas only. No medical complications at trial entry. Women were recruited from clinics while attending outpatient prenatal care Sample size calculation determined 26 women needed per group. 52 women randomised; data for 48. 2 women from each arm lost to follow-up
Interventions	Oral calcium 600 mg (1 capsule twice daily) versus oral placebo 600 mg (twice daily)
Outcomes	Concentrations of plasma ionised calcium and concentration of the free intracellular calcium concentration only
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence. Randomisation for all 3 sites conducted centrally
Allocation concealment (selection bias)	Low risk	Randomisation conducted centrally. Allocation concealed in sealed, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women and staff were unaware of treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Staff blind to treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 (8.4%) women lost to follow-up in each treatment group. Authors state that these exclusions did not modify the results
Selective reporting (reporting bias)	Low risk	Prespecified outcomes are reported.
Other bias	Low risk	None detected.

Methods	This study reports on a subset of women. The entire sample is reported in Goldberg 2013 above. Jarjou 2006 and Goldberg 2013 do not report the same outcomes, so there is no duplication of participants in this review's analysis Type of study: a randomised, double-blind, placebo-controlled study. Method of treatment allocation: participants were randomly assigned in double-blind fashion to receive calcium or placebo by using block of 4 from published sets of tables in each month and thereby to minimise the potential for seasonal confounding. The code was held by a member of study team who was not directly involved with the collection of data in the field or laboratory and who had no contact with the study participants. Stratification: not stated. Placebo: yes, starch tablets. Sample size calculation: not stated. Intention-to-treat analyses: no, final analyses were 61 from 77 in treatment group, 64 from 78 in control group. Losses to follow-up: 19.3 % (30 in 155).	
Participants	Location: Gambian women, in rural village of Keneba and Manduar, in the province of West King. Time frame: May 1995 to June 1999. Eligible criteria: nulliparity with no history of any medical condition known to affect calcium or bone metabolism, normal single viable pregnancy with known menstrual period date (LMP), registering at antenatal clinic before 20 weeks of gestation and intended to undergo delivery at the same institution, normal glucose tolerance test and willing to participate in trial, first antenatal visit BP below 140/90 mmHg and free of any underlying medical disorders, based on a comprehensive medical examination and routine laboratory tests Exclusion criteria: had history or evidence of renal disease, collagen vascular disease, chronic hypertension and endocrinological disease or if they took any medication. Total recruited: 155 pregnant women. Treatment group, n = 77 and control group, n = 78 women. In the final analysis only 125 mother-infant pairs were analysed (61 in the treatment group, 64 in the control group)	
Interventions	1500 mg of calcium (3 chewable tablets of calcium carbonate per day, 500 mg of elemental calcium). 3 tablets of placebo (contained microcrystalline cellulose and lactose) per day, same shape, taste and texture. The study started from 20 weeks until delivery	
Outcomes	1. Anthropometric measurement (weight, height of pregnant women and fetal birthweight, height, crown-heel, head circumference) in 24 hours postpartum. 2. Infant bone mineral density.	
Notes	Lost to follow-up of infants outcomes: 16 in treatment group; only 61 infants were analysed, 14 in control group; only 64 infants were analysed	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Quote: "Subjects were randomly assigned in double-blind fashion to receive calcium or placebo by using block of 4 to ensure that equal numbers of subjects were allocated to supplement and placebo groups in each month and thereby to minimize the potential for seasonal confounding. Randomization was achieved by using published sets of tables."
Allocation concealment (selection bias)	Low risk	Quote: "The code was held by a member of study team who was not directly involved with the collection of data in the field or laboratory and who had no contact with the study participants."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Subjects were randomly assigned in double-blind fashion to receive calcium or placebo by using block of 4. Treatment drug and placebo (contained microcrystalline cellulose and lactose) per day, same shape, taste and texture)." Women and staff blind to group assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The code was held by a member of study team who was not directly involved with the collection of data in the field or laboratory and who had no contact with the study participants." Anthropometric measurements collected by medical staff. Breast-milk calcium and phosphorus was collected and sent to laboratory centre. Maternal urine calcium also sent to central laboratory. Maternal calcium intake assessed by field workers
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "There were no significant differences between the 2 groups in supplementation period, or compliance." Flowchart reports attrition due to maternal (1), fetal or neonatal death (5), multiple pregnancy (4), miscalculation of gestation at trial entrance (19) and lost contact (1) Missing data 30 in 155 = 19.3%.
Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

Karandish 2003

Methods	Type of study: double-blind, placebo-controlled, randomised clinical trial Method of treatment allocation: no data. Placebo: yes (starch tablets). Intention-to-treat analyses: no, the initial number of participants were 77 pregnant women but by the end of study 68 participants remained. Losses to follow-up: 11.7 % (9 in 77).
Participants	Location: 2 prenatal clinics in county of Ahvaz, Iran. Time frame: no data. Eligible criteria: pregnant women between the ages of 18 to 35 Pregnant women in their third trimester before week 28 of their pregnancies No history of abortion or stillbirth. Not suffering from any metabolic or chronic diseases. Not having previous history of giving birth to twins. Not being on any other supplements with the exception of iron and folic acid Total recruited 77 pregnant women, treatment group, n = 33, placebo group, n = 35
Interventions	1000 mg of calcium (2 capsules of 500 mg calcium carbonate) compared with placebo. The study started from 28th-30th week gestation until delivery
Outcomes	Anthropometric parameters of neonates including weight, head circumference and length
Notes	This paper was written in Farsi. Dr Reza Navaei kindly translated it to English using the Cochrane Pregnancy and Childbirth Group's translation form

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Double-blind, placebo-controlled, randomised clinical trial were mentioned but there was no detail of sequencing generation
Allocation concealment (selection bias)	Unclear risk	No detail in allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Randomised controlled trial. Placebo made by Manufacturer as the calcium capsules. Blinding of participants and staff
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trial was double blind. Patients and clinic staff were unaware of type of medicine
Incomplete outcome data (attrition bias) All outcomes	High risk	The initial participants were 77 pregnant women but the final analyses were 68 women. No details about 9 women who dropped out from the study

Karandish 2003 (Continued)

Selective reporting (reporting bias)	Low risk	The preplanned outcomes were reported.
Other bias	Low risk	None identified.

Kumar 2009

Methods	Type of study: double-blinded randomised trial with simple randomisation sequence developed manually The blinding of study participants and investigators was done by assigning coded numbers to the package Method of treatment allocation: the packages were distributed to the participants using the random number in sequence Placebo: yes. Intention-to-treat analyses: no, only participants 524 who delivered in hospital. Losses to follow-up: 28 from 552 = 5.1% (17 in treatment group and 11 in placebo group)
Participants	Location: At Lok Nayak Hospital, New Delhi, India. Time frame: January 2005 and December 2007. Eligible criteria: healthy normotensive primigravidas with non complicated singleton pregnancy, 12-25 weeks' gestation Exclusion criteria: multiple pregnancy, polyhydramnios, fetal malformation, diabetes, chronic hypertension, renal disease, cardiovascular disease, urolithiasis or BP > 140/90 mmHg Total recruited 552 pregnant women, treatment group, n = 290, placebo group, n = 262
Interventions	Oral calcium carbonate 4 tablets daily (500 mg each) compared with placebo, 4 tablets daily, from GA 12-25 week until delivery
Outcomes	1. BP. 2. Maternal and neonatal outcomes including: pre-eclampsia, preterm delivery, induction of labour, CS, fetal distress during labour, meconium during labour, GA at delivery, gestational duration at delivery (wk; < 32, 32 to 36, 37 to 40, > 40), birthweight g, birthweight (kg < 2, 2 to 2.5, 2.5 to 4), small-for-gestational age, stillbirth
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Double-blinded randomised trial with simple randomisation sequence developed manually
Allocation concealment (selection bias)	Low risk	Allocation concealed by assigning treatment packages with code, which was unbroken until the end of the study. The pack-

Kumar 2009 (Continued)

		ages were distributed to the participants using the random number in sequence
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The blinding of study participants and investigators was done by assigning coded numbers to the package
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All women were followed up in prenatal clinic in a routine manner
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: 28 from 552 = 5.1% (17 in treatment group and 11 in placebo group)
Selective reporting (reporting bias)	Low risk	The preplanned outcomes were reported.
Other bias	Low risk	None identified.

Levine 1997

Methods	Type of study: double-blind, computer-generated simple randomisation sequence Method of treatment allocation: packages of study tablets were prepared and numbered by manufacturer and then shipped to the medical centre. Stratification: not stated. Placebo: yes, starch tablets. Sample size calculation: not stated. Intention-to-treat analyses: yes. Losses to follow-up: 253 in 4589 women (5.5%); 132 in the calcium group, 121 in the placebo group
Participants	Location: The Calcium for Preeclampsia Prevention (CPEP) Trial at 5 U.S medical centres Time frame: not stated. Eligibility criteria: nulliparity, normal single viable pregnancy with known menstrual period date (LMP), registering at antenatal clinic before 11 to 21 weeks of gestation and intended to undergo delivery at the same institution, normal glucose tolerance test and willing to participate in trial, BP below 134/84 mmHg and free of any underlying medical disorders, based on a comprehensive medical examination and routine laboratory tests. Exclusion criteria: taking medication, had bad obstetrical conditions, pre-existing disease, elevated serum concentration of creatinine (> 1.0 mg/dL) or calcium (> 10.6 mg /dL, pregnant women with renal disease, haematuria, or history of urolithiasis in themselves or in first-degree relative and who report frequently use of calcium supplementation or antacid Total recruited: 4589 pregnant women; treatment group n = 2295, control group n = 2294

Interventions	2 g of calcium (4 chewable tablets of calcium carbonate per day, 500 mg of elemental calcium), start at 13 to 20 weeks until delivery, 2 tablets with morning meal and 2 tablets with evening meal. Compared with 4 tablets of placebo (contained lactose and granulated starch) per day, same size, weight and colour
Outcomes	1. Incidence of PIH. 2. Pregnancy outcomes; preterm birth, premature rupture of membrane, birthweight, birth length, admission to NICU, perinatal losses. 3. Urolithiasis, renal insufficiency.
Notes	Koo 1999 was another subset report of Levine 1997. Total recruited: 289 pregnant women. 13 refused consent; only 256 women and 256 infants were included (128 in each group) 1. Fetal bone mineral density, bone mineral content. 2. Pregnancy outcomes; GA, birthweight, birth length, and head circumference.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Package of study tablets were prepared and numbered by manufacturer according to a computer-generated simple randomisation sequence developed by statisticians."
Allocation concealment (selection bias)	Low risk	Quote: "Package of study tablets were prepared and numbered by manufacturer according to a computer-generated simple randomisation sequence developed by statisticians and then were shipped to the medical centres. Upon enrolment, each woman was assigned the next number packages of medication at the centre and thus was randomised automatically to receive calcium or placebo according to the pre assigned random sequence."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind, calcium supplementation versus placebo. Package of study tablets were prepared and numbered by manufacturer according to a computer-generated simple randomisation sequence developed by statisticians. Women and staff blind to allocation."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All pregnant women received routines prenatal care. Staff blind to treatment"

Levine 1997 (Continued)

		allocation.”
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: “Of 4589 women enrolled in the study, 253 women (5.5%) were lost to follow-up; 132 in the calcium group, 121 in the placebo group.” Missing data 253 in 4589 = 5.5%.
Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

Lopez-Jaramillo 1989

Methods	Type of study: prospective, randomised, double-blind, controlled clinical trial Method of treatment allocation: table of random numbers. The containers and the calcium tablets for both groups were prepared in Facultad de Quimica y Farmacia Stratification: not stated. Placebo: yes, start tablets. Sample size calculation: not stated. Intention-to-treat analyses: yes. Losses to follow-up: 13.2%. Only women with no missing values for any of the covariate and outcome variables were included in the analysis. 49 in calcium group and 43 in placebo group. 6 women in calcium group and 8 in placebo group were eliminated from analysis because they were delivered before 38 weeks
Participants	Location: antenatal outpatient clinic in the Hospital Gineco-Obsterica Isidro Aroya in Quito, Ecuador Time frame: 30 months during 1984-1986. Eligible criteria: nulliparity, age < 25 years, certain LMP, registration at antenatal clinic for the first prenatal visit before 24 weeks' gestation and residency in Quito (2800 m altitude) for a period of at least 1 year before conception, BP < 120/80 mmHg and free for of any underlying medical disorders based on a comprehensive medical student examination and routine laboratory tests Exclusion criteria: had history of cardiovascular, renal or endocrinological disease or if they took any type of drug or vitamin/mineral preparation Total recruited: 106 pregnant women; n = 55 in treatment group, n = 51 in control group
Interventions	2000 mg of calcium (4 tablets of calcium gluconate daily, 500 mg of elemental calcium) compared with 4 tablets of placebo per day, same size, weight and colour. Started treatment at 23 weeks until delivery
Outcomes	1. BP develop PIH. 2. Pregnancy outcomes; weight gain, preterm birth, birthweight, perinatal mortality. 3. Serum ionised calcium concentrations.
Notes	

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Using a table of random numbers each patients was assigned independently in sequence to one of two treatment regimens."
Allocation concealment (selection bias)	Low risk	Quote: "The containers and the calcium tablets for both groups were prepared in Facultad de Quimica y Farmacia."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment versus placebo. All participants were blinded to intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The placebo group also received 4 tablets daily of the same size, weight, colour and organoleptic characteristics as calcium tablets
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "106 women satisfactory met the subject selection criteria. Only women with no missing values for any of the covariate and outcome variables were included in these statistical analysis. 49 in the calcium supplemented group and 43 in the placebo group. Six women in calcium supplement group and eight in the placebo group were eliminated from analysis because they were delivery before 38 weeks." Missing data 14 in 106 = 13.2%.
Selective reporting (reporting bias)	Unclear risk	Comment: not all enrolled participants were analysed.
Other bias	Low risk	None identified.

Lopez-Jaramillo 1997

Methods	Type of study: a prospective, randomised, double-blind, controlled clinical trial. Sequence according to random numbers table Method of treatment allocation: used a table of random numbers to assign each patient independently in sequence to 1 of 2 treatment regimens Treatment assignment was double-blind, with composition of tablets unknown to the patients and to all clinical personnel involved in the study. The containers and tablets were prepared in the Facultad de Quimica y Farmacia, Universidad Central del Ecuador Stratification: not stated. Placebo: yes, starch tablets. Sample size calculation: not stated. Intention-to-treat analyses: no. Losses to follow-up: yes, 14 in 274 = 5.1%.	
Participants	Location: Hospital Gineco-Obstetrico Isidro Ayora in Quito, Ecuador Time frame: 56-month period between 1990 to 1995. Eligible criteria: age < 17.5 years, nulliparity, normal single viable pregnancy with known menstrual period date (LMP), registering at antenatal clinic before 20 weeks of gestation, residency in Quito (2800 m altitude) for a period of at least 1 year before conception, BP < 120/80 mmHg and free from any underlying medical disorders, based on a comprehensive medical examination and laboratory test Exclusion criteria: had history of cardiovascular, renal or endocrinological disease or if they took any type of drugs or vitamin/mineral preparations Total recruited: 274 pregnant teenagers were randomised; 14 women failed to complete the protocol (3 changed residence, 7 changed to a private hospital, 2 changed to hospital of social insurance, 2 by non-compliance to treatment); only 260 completed the study, 125 girls received 2000 mg calcium, 135 girls in control group	
Interventions	2 g calcium (4 tablets of calcium carbonate per day, 500 mg of elemental calcium) compared with 4 tablets of placebo (contained lactose and granulated starch) per day, same size, weight, colour and organoleptic characteristics as calcium tablets	
Outcomes	1. Incidence of PIH. 2. Serum ionised calcium concentrations. 3. Pregnancy outcomes; GA, weight gain, birthweight, fetal mortality. 4. Side effects of calcium.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "We used a table of random numbers to assigned each patient independently in sequence to one of two treatment regimens."
Allocation concealment (selection bias)	Low risk	Quote: "The containers and tablets were prepared in the Facultad de Quimica y Far-

		macia, Universidad Central del Ecuador.”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “We used a table of random numbers to assigned each patient independently in sequence to one of two treatment regimens.” Quote: “Treatment assignment was double-blind, with the composition of the tablets unknown to the patients and to all clinical personnel involve in the study.”
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “Treatment assignment was double-blind, with the composition of the tablets unknown to the patients and to all clinical personnel involve in the study.”
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: “274 teenagers were randomised and then 14 women failed to completed the protocol (3 changed the residence, 7 changed to the private hospital, 2 changed to hospital of social insurance, 2 by non-compliance to treatment) then only 260 completed the study; 125 girls received 2000 mg calcium, 135 girls in the control group.” Missing data 5.1%. The authors did not provide information about how many people were missing in each group
Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

Niromanesh 2001

Methods	Type of study: double-blind, placebo-controlled clinical trial. Randomly assigned to 1 of 2 treatments Method of treatment allocation: the manufacturing company coded the tablets. The hospital pharmacy dispensed the tablet among the participants Stratification: not stated. Placebo: yes, starch tablet. Sample size calculation: not stated. Intention-to-treat analyses: yes. Losses to follow-up: 0%.
Participants	Location: Mirza-Kochak-Khan Gynecology Hospital, Tehran, Iran Time frame: not stated. Eligible criteria: high risk for pre-eclampsia, positive roll-over test, GA 28 to 32 weeks, BP < 140/90 mmHg. Exclusion criteria: negative for roll-over test and had any chronic condition such as

	diabetes, renal diseases, cardiovascular disease, hypertension, and severe anaemia. Total recruited: 30 women at high risk of pre-eclampsia (15 in the calcium group, 15 in the control group)
Interventions	2 g of calcium (4 tablets of 500 mg orally every 6 hours). Compared with placebo. Started treatment at 28 to 32 weeks.
Outcomes	1. Incidence of PIH. 2. Maternal weight gain. 3. Pregnancy outcomes; duration of pregnancy, birthweight.
Notes	No details about the type of calcium.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Thirty women at high risk of preeclampsia were randomly assigned to 2 g of calcium daily intake and placebo regimen." Comment: the method of sequence generation was not described
Allocation concealment (selection bias)	Low risk	Quote: "The manufactory company coded the tablets. The hospital pharmacy dispensed the tablet among the subjects."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Randomization and blinding of subjects and investigator were managed by providing coded tablets of the same packaging and physical characteristics for both calcium and placebo tablets."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Randomization and blinding of subjects and investigator were managed by providing coded tablets of the same packaging and physical characteristics for both calcium and placebo tablets." Blood pressure and proteinuria were evaluated in each visit
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "There was no loss to follow up in the course of study." Missing data = 0%.
Selective reporting (reporting bias)	Low risk	None identified.

Other bias	Low risk	None identified.

Purwar 1996

Methods	Type of study: randomised double-blind placebo-controlled trial Method of treatment allocation: the women were assigned randomly in a double-blind fashion to 1 of 2 treatment groups (calcium/placebo) using computer-generated random number table. All the containers and tablets were specially prepared by local Universal pharmaceutical, Nagpur Stratification: not stated. Placebo: yes, starch tablets. Sample size calculation: not stated. Intention-to-treat analyses: no. Losses to follow-up: yes, 11 in 201 = 5.5%.
Participants	Location: the Government Medical College and Hospital, Nagpur, India Time frame: October 1, 1993 to December 31, 1994. Eligible criteria: nulliparity, normal single viable pregnancy with known menstrual period date (LMP), registering at antenatal clinic before 20 weeks of gestation and intending to undergo delivery at the same institution, normal glucose tolerance test < 140 mg/dl and willing to participate in trial, first antenatal visit below 140/90 mmHg and free of any underlying medical disorders, based on a comprehensive medical examination and routine laboratory tests. Exclusion criteria: renal disease, collagen vascular disease, chronic hypertension, endocrinological disease or if on any medication Total recruited: 201 pregnant women; treatment group, n = 103, control group, n = 98. Final number for analysis (treatment group n = 97, control group n = 93)
Interventions	2 g calcium (4 tablets of 500 mg calcium carbonate). Placebo (4 tablets of placebo) same size, weight and colour
Outcomes	1. Incidence of PIH. 2. Pregnancy outcomes; preterm birth, birthweight, fetal growth restriction.
Notes	Missing data 11 in 201 = 5.5%.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The women were assigned randomly in a double-blind fashion at 20 weeks gestation to 1 of 2 treatment groups (calcium/placebo) using computer-generated random number table."

Purwar 1996 (Continued)

Allocation concealment (selection bias)	Low risk	Quote: "All the containers and tablets used were specially prepared for the study by local Universal Pharmaceutical Pvt Ltd, Nagpur."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The calcium supplemented group received 4 tablets of calcium (500 mg of elemental calcium each) for total 2 g and the placebo group received 4 tablets of the same size, weight, and colour."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Blood pressure were measured by one physician specially trained. Any ante/intrapartum maternal and fetal complications were recorded."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "A total of 98 women randomly assigned to the placebo groups and 103 in calcium groups. Eleven women (5.47%) were lost to follow-up after randomisation (5 in the placebo group and 6 in the calcium group). The total of 93 women in the placebo group and 98 women in the calcium group were included in the final analysis." Missing data 11 in 201 = 5.5%.
Selective reporting (reporting bias)	Unclear risk	None identified. There were inconsistent missing data. The number lost to follow-up is 11 from 201; 200 participants should have remained in the final analysis, but the given number included in final analysis was 201 participants
Other bias	Low risk	None identified.

Raman 1978

Methods	Type of study: pregnant women were assigned by strict rotation to 1 of 3 groups Method of treatment allocation: not clearly stated. Stratification: not stated. Placebo: no (no treatment). Sample size calculation: not stated. Intention-to-treat analyses: no. Losses to follow-up: 186 in 273 = 68.1%.

Participants	Location: India, poor segment of the population. Time frame: not stated. Eligible criteria: pregnant women who were in low-economic status and had regularly consumed supplements were enrolled. Exclusion criteria: pregnant women suffered from complications such as toxemia, hypertension and diabetes. Total recruited: 273 pregnant women divided into 3 groups.
Interventions	Calcium lactate was given in tablet form supplying 150 mg of elemental calcium per tablet. Started treatment at 18 to 22 weeks until delivery Group 1: control, n = 38 no treatment. Group 2: n = 25 received calcium 300 mg/d. Group 3: n = 24 received calcium 600 mg /d.
Outcomes	1. X-ray left hand (anteroposterior view) of mothers. 2. X-ray ulna, radius, tibia fibular of neonate. 3. Densitometry of metacarpal and 4-1 phalangeal of mothers. 4. Densitometry of ulna, radius, tibia fibular of neonate.
Notes	Comment: only 87 participants completed data: 38, 25, 24 participants in 3 groups respectively, high rate of losses to follow-up 186 in 273 = 68.1% For data in Analysis 2.4 the placebo n was halved to enable inclusion of data for treatment groups 1 and 2

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the women were assigned by strictly rotation to one of three groups" Comment: method of sequence generation was not stated.
Allocation concealment (selection bias)	Unclear risk	Comment: method of allocation concealment was not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Treatment versus no treatment. The participants were not blinded. The intervention was divided into 2 groups which unequal dosage
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unable to blind outcomes assessment due to different dosage and treatment
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Of the 273 mothers registered, data completed in all aspect, could be obtained in 87 subjects (38, 25, 24 respec-

Raman 1978 (Continued)

		tively” Comment: high rate of loss to follow-up. Missing data 186 in 273 = 68.1%. (in treatment group (calcium 300 mg/d) = 72.5%; in treatment group (calcium 600 mg/d) = 73.6%; in control group = 58.2%).
Selective reporting (reporting bias)	Unclear risk	Unclear.
Other bias	Low risk	None identified.

Rogers 1999

Methods	Type of study: randomised trial. Method of treatment allocation: unsealed envelopes. Stratification: not stated. Placebo: no (no treatment). Sample size calculation: not stated. Intention-to-treat analyses: yes. Losses to follow-up: 18 in 237 =7.6%.	
Participants	Location: Chinese Women's Hospital, Hong Kong. Time frame: July 1992 to December 1994. Eligible criteria: normotensive, MAP > 80 and < 106 mmHg, second trimester, singleton and used cutoff value 60 mmHg of left lateral position. Exclusion criteria: MAP < 60 mmHg. Total recruited: 500 pregnant women (131 patients were excluded only 369 patients were randomised),154 in calcium group, 132 in low-dose aspirin, 83 in control group.	
Interventions	Compared 3 groups of total 369 patients. 1. Calcium (154 patients) 600 mg/day from 22 to 32 weeks and 1200 mg/d in dividing dose from 32 weeks to delivery. 2. Low dose aspirin (132 patients) 80 mg/d starting at 22 weeks until delivery. 3. Control group were no treatment in 83 patients.	
Outcomes	1. Mean arterial BP. 2. Pregnancy outcomes; GA, birthweight, Apgar score. 3. Incidence of proteinurics and non proteinurics PIH.	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was into three groups: control, low-dose aspirin, and calcium supplementation in a ratio of 1:2:2 using five unsealed envelopes." Of 500 nulliparous women screened, 369 were randomised; 154 were in calcium group, 132 were in low-dose aspirin and 83 as control group."
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization was into three groups; control, low-dose aspirin, and calcium supplementation in a ratio of 1:2:2 using five unsealed envelopes."
Blinding of participants and personnel (performance bias) All outcomes	High risk	The participants received different interventions. Could not blind both participants and assessors
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "All randomisation, data collection and data entry were undertaken by the same research assistant with the exception of outcome data, which were entered by the first two authors. The research assistant was therefore blind to the outcome group." It is unclear whether the authors collecting data would have been aware of group assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Fifty (10%) patients eventually delivered in other hospitals and were therefore not subjected to analysis, as they could not reliably be classified into the 3 outcomes groups. 144, 118, and 75 were in calcium group, low-dose aspirin, and control groups respectively were included in final analysis." Missing data 18 in 237 = 7.6%.
Selective reporting (reporting bias)	Unclear risk	None identified.
Other bias	Low risk	None identified.

Sanchez-Ramos 1994

Methods	Type of study: randomised double-blind, placebo-controlled clinical trial Method of treatment allocation: women with positive angiotensin test were randomised by means of a computer-generated list. Calcium and placebo tablets were provided by pharmaceutical company Stratification: not stated. Placebo: yes, placebo. Sample size calculation: not stated. Intention-to-treat analyses: no. Losses to follow-up: 4 in 67 = 6.0%. Post randomised exclusion: 6 in 67 = 8.9 % did not comply fully with the protocol; 4 were excluded from analysis after randomisation because of a lack of information, 1 was admitted to another hospital (in placebo group), another woman refused to participate after 1 week of trial (in calcium group)	
Participants	Location: University of Florida Health Science Center, Jacksonville, Florida Time frame: January 1, 1989 to July 30, 1993. Eligible criteria: normotensive, nulliparous with increased risk of PIH with positive angiotensin sensitivity test only who were positive roll-over test (women supine diastolic BP value were more than 20 mmHg higher than those obtained on her side) received angiotensin infusion at 24 to 28 weeks Exclusion criteria: participants with conditions known to increase the incidence of PIH, including history or evidence of renal disease, collagen vascular disease, diabetes mellitus, chronic hypertension and multiple pregnancy Total recruited: 281 pregnant women were positive roll-over test; 67 women positive angiotensin sensitivity test; 33 received calcium, 34 received placebo. Final analyses, calcium group, n = 29, control group, n = 34	
Interventions	2 g of calcium carbonate, compared with placebo (contained starch and were identical to calcium tablets with respected to weight, size, flavour and appearance)	
Outcomes	1. Incidence PIH. 2. Pregnancy outcomes; GA, preterm birth, birthweight, Apgar score, NICU admission, fetal growth restriction, perinatal death.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Women with positive angiotensin test were randomised by means of a computer-generated list to receive either 2 g/day of elemental calcium or matching placebo." "
Allocation concealment (selection bias)	Low risk	Quote: "Calcium and placebo tablets were provided by pharmaceutical company."

Sanchez-Ramos 1994 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment versus placebo. All participants were blinded to intervention. Placebo contained starch and were identical to calcium tablets with respect to weight, size, flavour and appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigators were blinded to treatment. Placebo tablets contained starch and were identical to calcium tablets with respect to weight, size, flavour and appearance
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Six women (8.9%) did not comply fully the protocol; of these, four were excluded from analysis after randomisation because lack of information. One had a single follow-up prenatal visited and refused to continue participating in the study. She was admitted to another hospital at 35 weeks' gestation with severe preeclampsia and required labour induction (in placebo group) . Another woman refused to participate after one week of trial (in calcium group)." Missing data 4 in 67 = 6%.
Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

Sanchez-Ramos 1995

Methods	Type of study: computer-generated list of random numbers. Method of treatment allocation: the randomisation list was maintain by pharmaceutical personnel. The drug and placebo were delivered by pharmacy to antepartum ward, where a nurse administered the medication Stratification: not stated. Placebo: yes, starch tablets. Sample size calculation: not stated. Intention-to-treat analyses: no, because of a decline in perinatal research support, the study was terminated 3 cases earlier than suggested by power analysis Losses to follow-up: 0%.
Participants	Location: University Medical Center, Jacksonville, Florida, USA Time frame: July 1990 - January 1993. Eligible criteria: nulliparity, 24 to 36 weeks' gestation, mild pre-eclampsia and no evidence of severe pre-eclampsia within 48 hours of admission Exclusion criteria: proteinuria > 5 g/d, platelet count < 100,000, oliguria (urine < 500 mL/d), pulmonary oedema, elevated liver enzyme > 200 U/L, microangiopathic haemo-

	dynamic anaemia, fetal growth retardation, known sensitivity to calcium, chronic hypertension, chronic renal disease, diabetes mellitus, or calcium supplement before admission Total recruited: 75 eligible participants; 36 in treatment group, 39 in control group (because of a decline in perinatal research support, the study was terminated 3 cases earlier than suggested by power analysis)	
Interventions	2 g of calcium/d (4 tablets of calcium carbonate per day, 500 mg of elemental calcium). Placebo (4 tablets of placebo per day, same size, weight and colour)	
Outcomes	1. Incidence of severe pre-eclampsia. 2. Pregnancy outcomes; GA, birthweight, Apgar score, fetal growth restriction, perinatal death. 3. Umbilical arterial blood gas.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were assigned using a computer-generated list of random number to receive either calcium or matching placebo."
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation list was maintained by pharmacy personnel; the drug and placebo were delivered by pharmacy to antepartum ward, where nurse administered the medication."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment versus placebo. All participants were blinded to intervention. Placebo tablets contained starch and were identical to calcium tablets with respect to weight, size, flavour and appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigators were blinded to treatment. Placebo tablets contained starch and were identical to calcium tablets with respect to weight, size, flavour and appearance
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "During the studied period, 75 eligible subjects were identified and invited to participate; 36 (48%) were assigned to calcium and 39 (52%) to placebo. Because of decline in perinatal research support, the study was terminated three cases earlier

		than suggested by power analysis.” Missing data = 0%.
Selective reporting (reporting bias)	Low risk	Trial was stopped before complete enrolment due to decline of research fund
Other bias	Low risk	None identified.

Taherian 2002

Methods	Type of study: randomised controlled study. Method of treatment allocation: the sampling method was non probability convenience. Used table of random numbers to assign each case independently to 1 of 3 groups Stratification: not stated. Placebo: no (no treatment). Sample size calculation: not stated. Intention-to-treat analyses: yes. Losses to follow-up: 0%.	
Participants	Location: Isfahan Health Centre, Iran. Time frame: April 1998 to March 2001. Eligible criteria: nulliparity, single gestation, first antenatal visit before 20 weeks of gestation, BP < 130/80 mmHg and no proteinuria by urine dipstick. Exclusion criteria: had history of cardiovascular, renal disease or endocrinologic problem, medical or obstetric complications and those with known hazardous condition (multiple gestation, hydatidiform mole). Total recruited: 990 healthy pregnant women (n = 330 participants/group)	
Interventions	Group 1: received 75 mg aspirin /day, n = 330. Group 2: received 500 mg calcium carbonate/day, n = 330. Group 3: no treatment as control group, n = 330. Started treatment at 20 weeks until delivery.	
Outcomes	1. BP. 2. Pregnancy outcomes; GA, birthweight, preterm birth, Apgar score, fetal growth restriction, perinatal death.	
Notes	Comment: the results were reported as mean and 95% CI; we changed them into SD	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “The sampling method was non probability convenience. We used table of random numbers to assign each case independently to one of three groups.”

Taherian 2002 (Continued)

Allocation concealment (selection bias)	Unclear risk	Comment: the method of allocation concealment was not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Group 1 received 75 mg aspirin; group 2 received 500 mg oral calcium-D daily; and the control group 3 received no medication at all." Comment: it was impossible to blind because the difference between drug and no treatment in control group
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "All cases received prenatal care according to the approved model, BP, body weight and maternal height were measured." Comment: assessors were not blinded because the participants received different treatments
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all enrolled participants were included in the analyses Missing data = 0%.
Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

Villar 1987

Methods	Type of study: double-blinded, randomised controlled clinical trial Method of treatment allocation: the women were assigned randomly in the double-blind fashion at 26 weeks' gestation to 1 of 2 treatment groups, using a randomisation schedule prepared in advance for the complete population. Stratification: not stated. Placebo: yes, starch tablets. Sample size calculation: not stated. Intention-to-treat analyses: yes. Losses to follow-up: 0%.
Participants	Location: The Johns Hopkins Hospital in Baltimore and Perinatal Study Center of Rosario, Argentina Time frame: 1983 to 1985. Eligible criteria: nulliparous, singleton, known LMP, age 18 to 30 years, free from any underlying medical disorders, negative roll-over test. Exclusion criteria: history of cardiovascular or renal disease or taking any drug. Total recruited: 52 pregnant women: *18 white: 9 in calcium group, 9 in placebo group; *34 black women: 16 in calcium group, 18 in placebo group.

	Total in calcium group, n = 25; in placebo group, n = 27.	
Interventions	3 tablets of calcium carbonate (500 mg each). Compared with 3 placebo tablets with same size, weight, size, colour and organoleptic characteristics. Started treatment at 26 weeks.	
Outcomes	1. Incidence of PIH. 2. Birthweight.	
Notes	Comment: the authors provide only mean birthweight but not SD. SDs in both groups were imputed by mean	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The women were assigned randomly in the double blind fashion at 26 weeks gestation to one of two treatment groups, using a randomisation schedule prepared in advance for the complete population."
Allocation concealment (selection bias)	Low risk	Quote: "The same randomization code, standardization process, and tablets were used in both populations and code was kept in central allocation (Baltimore). Random number in closed envelopes and corresponding medication were distributing to the two hospitals at the beginning. All containers and tablets were prepared by pharmaceutical."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The women were assigned randomly in the double blind fashion at 26 weeks gestation to one of two treatment groups, using a randomisation schedule prepared in advance for the complete population." Quote: "Placebo same size, weight, size, colour and organoleptic characteristic."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All BP value were measured by one nurse-midwife and one physician especially recruited and trained for the study." Comment: not specifically stated that outcome assessors were blinded, but placebo and treatment were identical

Villar 1987 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all enrolled participants were included in the analyses Missing data = 0%.
Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

Villar 1990

Methods	Type of study: double-blind, randomised placebo-controlled clinical trial Method of treatment allocation: computer-generated list of random number. Opaque envelopes with the bottle number were located at the clinic and the project co-ordinator was in charge of the administration of the treatment assigned. Stratification: not stated. Placebo: yes, starch tablets. Sample size calculation: not stated. Intention-to-treat analyses: yes. Losses to follow-up: 0%.	
Participants	Location: Adolescent Pregnancy Clinic of the Johns Hopkins Hospital in Baltimore Time frame: 1985 to 1988. Eligible criteria: age < 17 year, GA < 20 week, singleton pregnancy, certain LMP, free from any underlying medical disorders determined by history, physical examination, and laboratory tests Exclusion criteria: underlying medical disorders determined by history, physical examination, and laboratory tests Total recruited: 190 adolescent pregnant women; 95 in the calcium group, 95 in the placebo group	
Interventions	2 g of calcium (4 tablets of calcium carbonate per day, 500 mg of elemental calcium) compared with 4 tablets of placebo (contained lactose and granulated starch) per day, same size, weight and colour. Started treatment at 20 weeks until delivery	
Outcomes	1. Incidence of preterm labour. 2. Incidence of low birthweight, IUGR, premature rupture of membrane, PIH. 3. Pregnancy outcomes; GA, birthweight, birth length. 4. Incidence of bacteriuria, pyelonephritis.	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A computer-generated list of random number was used to allocate the corresponding treatments."

Allocation concealment (selection bias)	Low risk	Quote: "Opaque envelope with the bottle number were locate at the clinic and project coordinator was in charge of the administration of the treatment assigned."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment versus placebo. All participants were blinded to interventions. Placebo was the same size, weight, colour, and had the same organoleptic characteristics as the calcium tablets
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo was he same size, weight, colour, and had the same organoleptic characteristics as the calcium tablets. The investigators were blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all enrolled participants were analysed. Missing data = 0%.
Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

Villar 2006

Methods	Type of study: multicentre, randomised, placebo-controlled, double-blind trial. Central randomisation at WHO Geneva Method of treatment allocation: computer-generated random number blocking with randomly varying groups of 6 to 8 women and were used to restrict randomisation in the strata (country). The technique consisted of allocating consecutively numbered treatment boxes for each woman. Randomisation codes remained at the WHO Clinical trial Unit until the time of analysis and were not available to any person until the analyses were completed. Boxes and tablets were prepared and numbered by Magistra SA, GENEVA and were shipped to each centre. Stratification: yes, by country. Placebo: yes, starch tablets. Sample size calculation: not stated. Intention-to-treat analyses: yes. Losses to follow-up: 13 in 8325 = 0.16%. Before treatment started, 2 women in the calcium group were not pregnant. 2 women in the placebo group were excluded from the analyses 143 (3.4%) in calcium group (4157-143) were lost to follow-up and no delivery information; 4008 pregnancies available for analyses. 155 (3.7%) in placebo group (4168-155) lost to follow-up and no delivery information; 4006 pregnancies available for analyses of preterm labour and 4161 pregnancies available for analyses of PIH (final analyses) of preterm labour and 4151 pregnancies available for analyses of PIH (final analyses) Post randomised exclusion: 4 in calcium were not pregnant, 5 in placebo group
Participants	Location: Rosاريو, Argentina; Assiut , Egypt; Nagpur and Vellor, India; Lima, Peru; Johannesburg, South Africa; Ho Chiminh City, Vietnam; where population intake calcium < 600 mg/d Time frame: November 2001 to July 2003. Eligible criteria: healthy nulliparity, normal single viable pregnancy with known menstrual period date (LMP), registering at antenatal clinic before 20 weeks of gestation. Exclusion criteria: BP > 140/90 mmHg, had history or evidence of chronic hypertension, renal disease, signs and symptoms of nephrolithiasis, parathyroid disease and disease that require digoxin, phenytoin, or tetracycline therapy Total recruited: 8325 pregnant women were randomised, treatment group, n = 4157, control group, n = 4168
Interventions	1.5 g of calcium carbonate (1 x 500 mg tablet, 3 times per day at meal time), chewable tablets started at 20 weeks until delivery, and > 3 hours after any iron supplement. Compared with 3 tablets of placebo (contained lactose, sorbitol, cellulose plus other calcium free ingredient) per day, same form, colour and taste
Outcomes	1. Incidence of pre-eclampsia/eclampsia. 2. Pregnancy outcomes; GA, preterm birth, birthweight, birth length, maternal admission to intensive care unit, maternal death, stillbirth, neonatal death.
Notes	
<i>Risk of bias</i>	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Central randomisation at WHO Geneva. Computer-generated random number blocking with randomly varying groups of 6 to 8 women and were used to restrict randomisation in the strata (country)."
Allocation concealment (selection bias)	Low risk	Quote: "The technique consisted of allocating consecutively numbered treatment boxes for each woman. Randomization codes remained at the WHO Clinical trial Unit until the time of analysis and were not available to any person until the analyses were completed. Boxes and tablets were prepared and numbered by Magistra SA, GENEVA and were shipped to each centre."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Women were assigned randomly to receive calcium tablets or placebo. They were identical in form, color and taste." Randomisation code kept until study end
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Women were assigned randomly to receive calcium tablets or placebo. They were identical in form, color and taste." Blood pressure was recorded by trained nurses and doctors. Randomisation code kept until study end
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of 8325 women assigned randomly to group, 4157 were assigned to the calcium group and 4168 were assigned to the placebo group. Nine women (5 in the placebo group; 4 in calcium group) were determined to not be pregnant, and 2 women from each group who were lost to follow-up before starting any treatment were excluded from all analyses. Delivery information was unavailable for 143 (3.4%) in the placebo group; therefore, they did not contribute to the preterm analyses, but the available data were included in the analyses for other outcomes. Thus, 4151 women in the calcium group and 4161 women in the placebo group contribute to

Villar 2006 (Continued)

		the final analyses.” Missing data 13 in 8325 = 0.16%.
Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

Wanchu 2001

Methods	Type of study: randomly assigned to 2 treatment groups. Method of treatment allocation: not stated. Stratification: not stated. Placebo: no (no treatment). Sample size calculation: not stated. Intention-to-treat analyses: no. Losses to follow-up: 20 in 120 = 16.7%.
Participants	Location: Post Graduate Institute of Medical Education and Research, Chandigarh. Time frame: not stated. Eligible criteria: uncomplicated normotensive primigravida with singleton pregnancy, GA < 20 weeks. Exclusion criteria: multiple pregnancy, molar pregnancy, hydramnios, congenital malformation, chronic hypertension, chronic renal disease, diabetes mellitus and those already on calcium supplementation. Total recruited: 120 pregnant women were enrolled, 100 who completed the protocol were analysed. 50 participants in treatment group, 50 participants in control group
Interventions	2 g of calcium (4 tablets of calcium carbonate). Compared with no treatment. Started treatment at 20 weeks
Outcomes	1. Incidence of PIH. 2. Pregnancy outcomes; GA, PROM, preterm birth, birthweight, IUGR, Apgar score.
Notes	No restriction was put on dietary calcium intake in either group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “Patients were randomly assigned to either group of two treatment groups.” Comment: the method of sequence generation was not stated.
Allocation concealment (selection bias)	Unclear risk	Comment: the method of allocation concealment was not stated

Blinding of participants and personnel (performance bias) All outcomes	High risk	Treatment versus no treatment. Could not blind participants.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Could not blind investigator due to different treatment.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "120 pregnant women were enrolled in the study, 100 women who completed the protocol were analysed." Missing data = 20 in 120 = 16.7%.
Selective reporting (reporting bias)	Unclear risk	None identified.
Other bias	Low risk	None identified.

BP: blood pressure

Ca: calcium

CI: confidence interval

CS: caesarean section

g: gram

g/d: grams per day

GA: gestational age

ITT: intention-to-treat

IUGR: intrauterine growth restriction

LMP: last menstrual period

MAP: mean arterial pressure

NICU: neonatal intensive care unit

mg: milligram

mL/d: millilitres per day

mmHg: millimetres mercury

PIH: pregnancy-induced hypertension

PROM: preterm rupture of the membranes

SD: standard deviation

U/L: units per litre

WHO: World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Almirante 1998	This trial was reported in abstract form only. We emailed the authors for further information at the last publication of the review (2011) and have had no reply. The study has been excluded for insufficient information
Asemi 2012	The intervention was not relevant. The intervention was a combination of calcium and vitamin D supplementation. The study population was at risk for pre-eclampsia. The intervention took place in the third trimester. For these reasons the trial was excluded
Chames 2002	This trial was reported in abstract form only. We emailed the authors for further information at the last publication of the review (2011) and have had no reply. The study has been excluded for insufficient information
Diogenes 2013	The intervention was not relevant. The intervention for this trial was a combination of calcium and vitamin D
Duggin 1974	The outcomes were not relevant and allocation to groups was not random. 7 primiparas (aged 16-19 years) who were at 32-36 weeks' gestation were included. The participants were divided into control participants (patient 1-4) and supplemented participants (patients 5-7) to measure metabolic balance
Felix 1991	There was no random allocation to groups in this trial (women allocated to groups in sequence). The aim of the study was to examine the hypotensive effects of calcium in Andean women
Galimberti 2001	This trial was reported in abstract form only. We emailed the authors for further information at the last publication of the review (2011) and have had no reply. The study has been excluded for insufficient information
Hammar 1981	The participants were not appropriate. This study was aimed to determine the effect of calcium treatment in pregnant women who suffered from leg cramps; 42 pregnant women who suffered from leg cramps with gestational age 21-38 weeks were included
Janakiraman 2003	This was a cross-over study examining bone resorption among pregnant women during received calcium supplementation. 32 pregnant women gestational age 25-35 weeks participated in the study for 20 days. Each women received 1200 mg calcium supplement for 10 days and multivitamin without calcium for 10 days. N-telopeptides of type I collagen (NTX), a biomarker of bone resorption were measured
Kalkwarf 1997	The intervention was not appropriate. The study aimed to examine the effect of calcium supplementation on bone density in postpartum period. The randomised, placebo-controlled trial of 1 g calcium supplementation was conducted in 97 lactating and 99 non-lactating women a mean 16 ± 2 days postpartum (the study of lactation). The other trial (the study of weaning) 95 lactating women who weaned their infants in 2 months after enrolment and 92 non-lactating women were enrolled 5.6 ± 0.8 months postpartum
Kent 1995	The participants were not appropriate. This was a study focusing on the postpartum period and women were not randomised to receive calcium until 36 weeks' gestation. This trial aimed to study the effect of an oral calcium supplement on regional bone loss in normal lactation women. 79 pregnant women at gestational age 36 weeks were randomised to received placebo or 500 mg twice daily of calcium through to 24 weeks' lactation

(Continued)

Liu 2011	The intervention was not appropriate. The participants were provided calcium supplementation until 6 weeks postpartum and measured bone mineral density post-treatment
Lopez-Jaramillo 1990	The participants were not appropriate. The study aimed to examine the effect of calcium supplementation on risk of PIH in pregnant women who had a positive roll-over test
Mahomed 2000	The participants were not appropriate. The study aimed to examine the effect of calcium supplementation on risk of PIH and preterm labour in twin pregnancy
Mazurkevich 2013	This intervention was not relevant. The intervention in this study was a combination of calcium carbonate and cholecalciferol
Mukherjee 1997	The participants were not appropriate. The study aimed to examine the effect of calcium supplementation in reducing leg cramps in homogeneous Chinese population. All pregnant women who suffered from leg cramps during January 1994 and May 1995 were enrolled to receive either calcium gluconate 600 mg twice daily or 2 multivitamin tablets twice daily
Odendaal 1974	The participants were not appropriate. Calcium was supplemented only when participants suffered from leg cramps, which not relevant to the objective of the review
Prentice 1995	This study did not examine calcium supplementation amongst pregnant women. 60 Gambian mothers consuming a low-calcium were randomised to receive calcium supplement or placebo from 10 days to 78 weeks postpartum
Qui 1999	The intervention was not relevant. Calcium was supplemented from 20 weeks' gestation to postpartum 45 days
Robinson 1947	The intervention was not appropriate. Calcium was given to treat women with leg cramps, which was not relevant to the objective of the review

g: grams

PIH: pregnancy-induced hypertension

Characteristics of studies awaiting assessment [ordered by study ID]

Aghamohammady 2010

Methods	Randomised controlled trial.
Participants	Healthy pregnant women age > 35. Nulliparous only, between 15-20 weeks' gestation
Interventions	2 g daily elemental calcium versus 2 g daily placebo.
Outcomes	Preterm delivery, pre-eclampsia.

Aghamohammady 2010 (Continued)

Notes	This trial is reported in abstract form only with no outcome data. We have emailed the authors for additional information and outcome data

Sulovic 2013

Methods	Randomised controlled trial.
Participants	Healthy nulliparous pregnant women between 14-23 weeks' gestation
Interventions	Daily treatment with 2 g elemental calcium versus daily treatment with placebo
Outcomes	Incidence of pre-eclampsia, PIH, preterm deliveries, small for gestational age births, fetal or neonatal deaths
Notes	This trial is reported in abstract form only. We have emailed the authors for additional outcome data

Zheng 2000

Methods	Randomised controlled trial.
Participants	Pregnant women with gestation 20-34 weeks.
Interventions	Osteoform capsules 2 tablets daily (dosage not stated) vs no treatment
Outcomes	Serum calcium level, symptoms, PIH, IUGR.
Notes	This trial is reported in Chinese language only and has been sent for translation

Ca: Calcium

g/d: grams per day

IUGR: intrauterine growth restriction

PIH: pregnancy-induced hypertension

DATA AND ANALYSES

Comparison 1. Calcium supplementation versus placebo or no treatment (maternal outcomes)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Preterm birth (a) Birth prior to 37 weeks	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Main analysis	13	16139	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.70, 1.05]
1.2 Sensitivity analysis by concealment allocation	11	15379	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.65, 0.99]
2 Preterm birth (a) Birth prior to 37 weeks by dose of calcium	13	16139	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.70, 1.05]
2.1 Low dose	1	660	Risk Ratio (M-H, Random, 95% CI)	1.55 [1.00, 2.41]
2.2 High dose	12	15479	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.66, 0.99]
3 Preterm birth (a) Birth prior to 37 weeks by started to take calcium	13	16073	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.69, 1.05]
3.1 Started calcium before 20 weeks	5	13290	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.76, 1.11]
3.2 Started calcium at 20 weeks or more	8	2783	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.45, 1.15]
4 Preterm birth (a) Birth prior to 37 weeks by type of calcium	13	16139	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.70, 1.05]
4.1 Carbonate	12	16047	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.70, 1.05]
4.2 Lactate	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 Gluconate	1	92	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Preterm birth (b) Birth prior to 34 weeks	4	5669	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.80, 1.36]
6 Preterm birth (b) Birth prior to 34 weeks - Sensitivity analysis by concealment allocation	3	5569	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.79, 1.35]
7 Maternal weight gain (g/w)	3	404	Mean Difference (IV, Random, 95% CI)	-29.46 [-119.80, 60.89]
8 Maternal bone mineral density (g/cm ²) - First phalanx (calcium 300 mg)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9 Maternal bone mineral density (g/cm ²) - Second metacarpal (calcium 300 mg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10 Maternal bone mineral density (g/cm ²) - Fourth metacarpal (calcium 300 mg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11 Maternal bone mineral density (g/cm ²) - First phalanx (calcium 600 mg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

12 Maternal bone mineral density (g/cm ²) - Second metacarpal (calcium 600 mg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13 Maternal bone mineral density (g/cm ²) - Fourth metacarpal (calcium 600 mg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
14 Maternal death	2	8974	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.06, 1.38]
15 Maternal admission to intensive care unit	1	8312	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.66, 1.07]
16 Vaginal birth	8	6916	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.99, 1.03]
17 Instrumental vaginal birth	2	675	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.66, 1.20]
18 Caesarean section	9	7440	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.89, 1.10]

Comparison 2. Calcium supplementation versus placebo or no treatment (infant outcomes)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Low birthweight (< 2500 g)	6	14162	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.81, 1.07]
2 Low birthweight (< 2500 g) by started to take calcium	6	14162	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.81, 1.07]
2.1 Started calcium before 20 weeks	3	13425	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.94, 1.03]
2.2 Started calcium at 20 weeks or more	3	737	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.23, 0.73]
3 Low birthweight (< 2500 g) by type of calcium	6	14162	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.81, 1.07]
3.1 Gluconate	1	92	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Carbonate	5	14070	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.81, 1.07]
4 Birthweight (g)	21	9202	Mean Difference (IV, Random, 95% CI)	56.40 [13.55, 99.25]
5 Perinatal mortality	8	15785	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.72, 1.06]
6 Stillbirth or fetal death	6	15269	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.72, 1.14]
7 Admission to neonatal intensive care unit	4	14062	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.94, 1.18]
8 Birth length (cm)	7	6389	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.25, 0.06]
9 Head circumference (cm)	3	460	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.36, 0.18]
10 Intrauterine growth restriction	6	1701	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.61, 1.13]
11 Neonatal bone mineral density (g/cm ²)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
11.1 Total body	2	300	Mean Difference (IV, Fixed, 95% CI)	0.00 [0.00, 0.01]
11.2 Midshaft radius	1	122	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.01, 0.01]
11.3 Lumbar spine	1	256	Mean Difference (IV, Fixed, 95% CI)	0.01 [0.00, 0.02]

Comparison 3. Calcium supplementation versus placebo or no treatment (adverse outcomes)

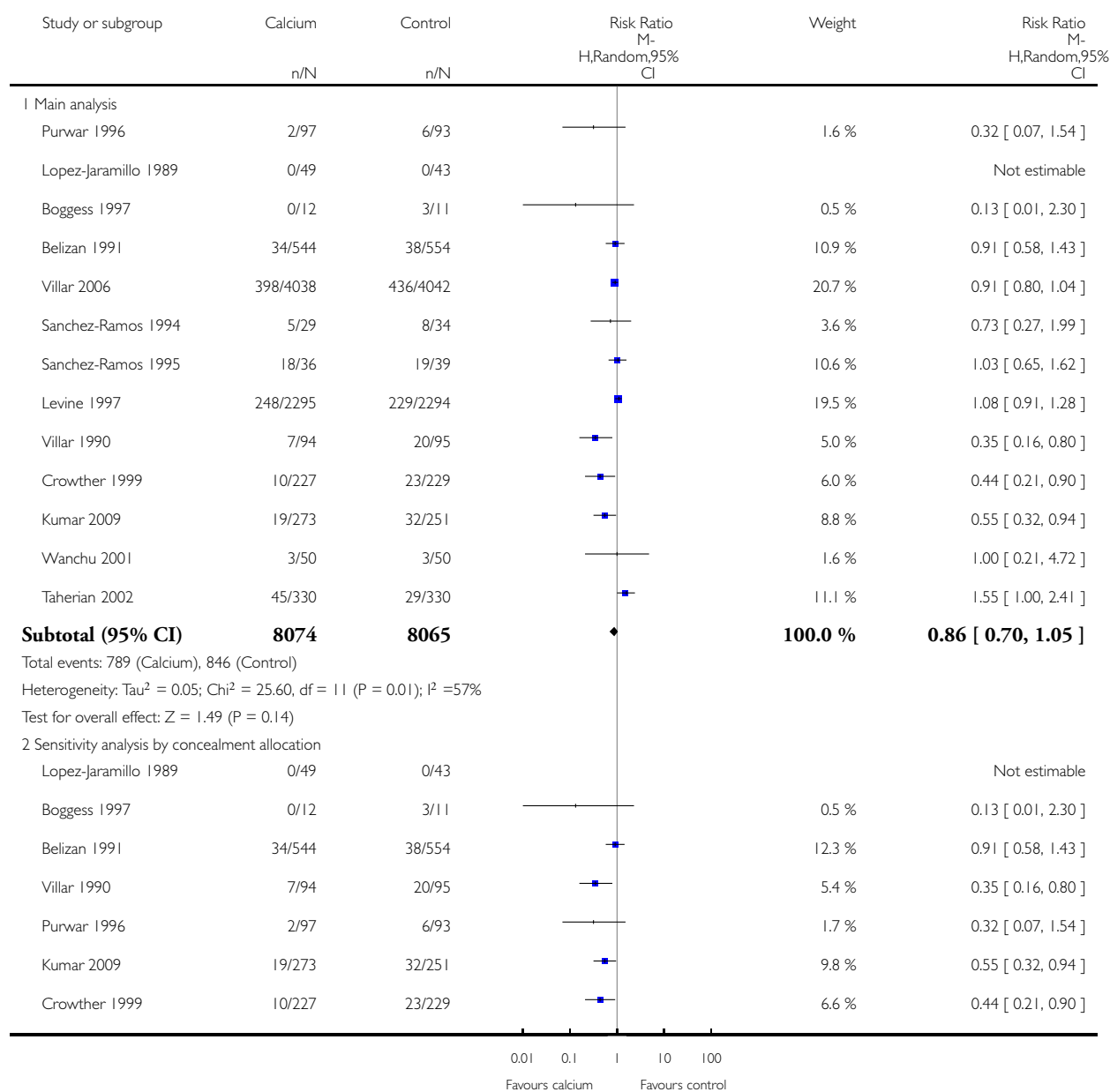
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Side effects of calcium supplementation - Maternal cholestatic jaundice	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Maternal cholestatic jaundice	1	100	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 71.92]
1.2 Gastrointestinal symptoms (including nausea, heartburn and diarrhoea)	1	52	Risk Ratio (M-H, Fixed, 95% CI)	2.16 [0.43, 10.78]
1.3 Gall stones	1	518	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.48, 3.85]
1.4 Headache, vomiting, backache, swelling, vaginal and urinary complaints, dyspepsia, abdominal pain	1	8312	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.93, 1.12]
2 Urinary stones	3	13419	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.48, 2.54]
3 Urinary tract infection	3	1743	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.69, 1.30]
4 Renal colic	1	8312	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.40, 6.99]
5 Impaired renal function	1	4589	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.51, 1.64]
6 Maternal anemia	1	1098	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.90, 1.22]

Analysis 1.1. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 1 Preterm birth (a) Birth prior to 37 weeks.

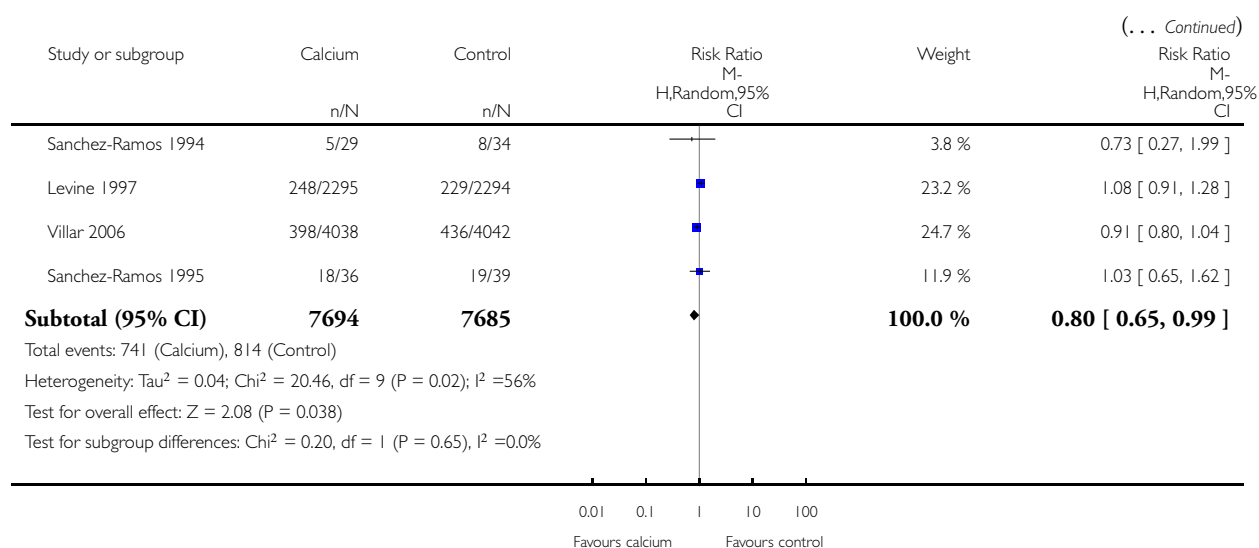
Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 1 Calcium supplementation versus placebo or no treatment (maternal outcomes)

Outcome: 1 Preterm birth (a) Birth prior to 37 weeks



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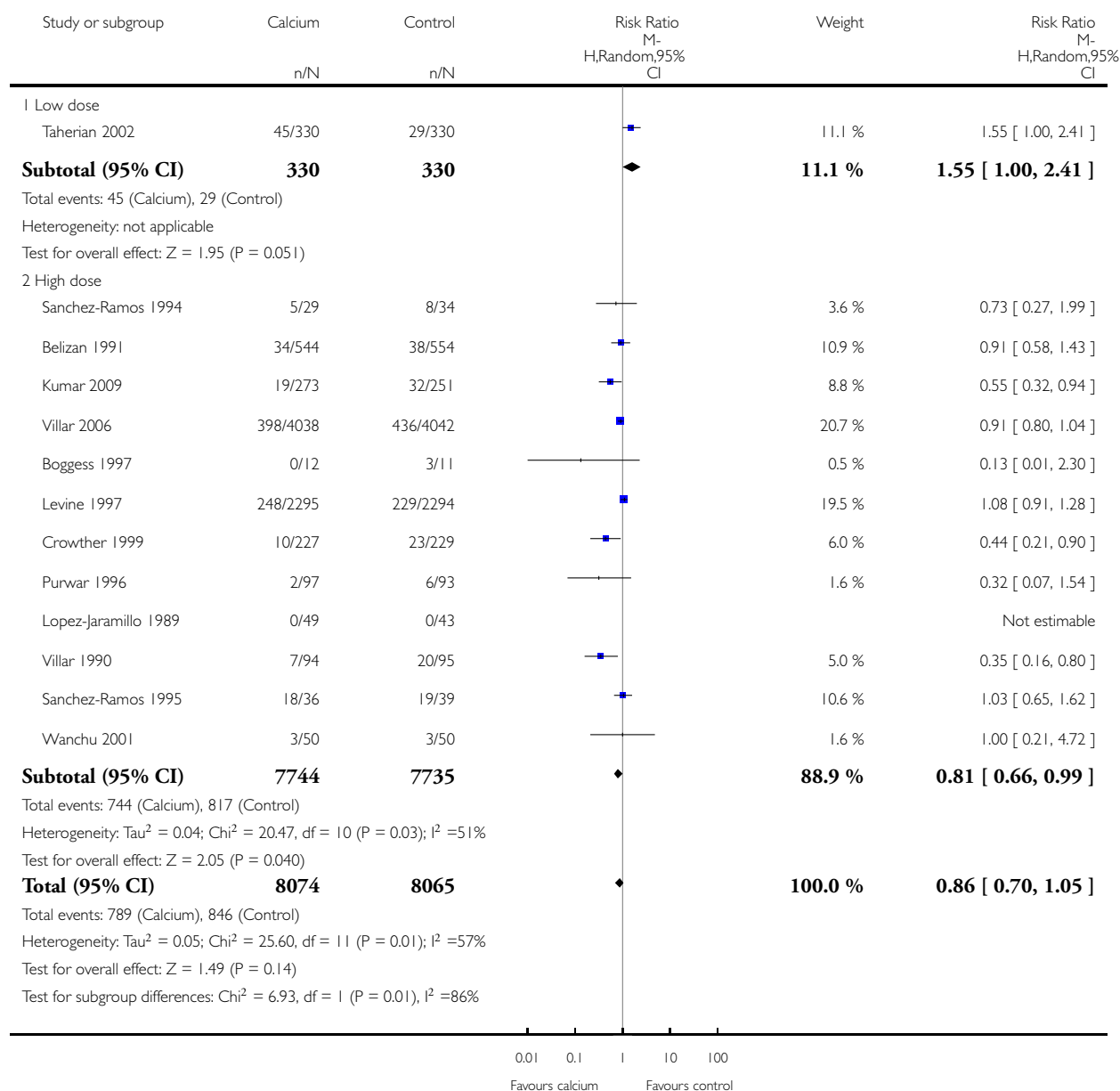


Analysis 1.2. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 2 Preterm birth (a) Birth prior to 37 weeks by dose of calcium.

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 1 Calcium supplementation versus placebo or no treatment (maternal outcomes)

Outcome: 2 Preterm birth (a) Birth prior to 37 weeks by dose of calcium

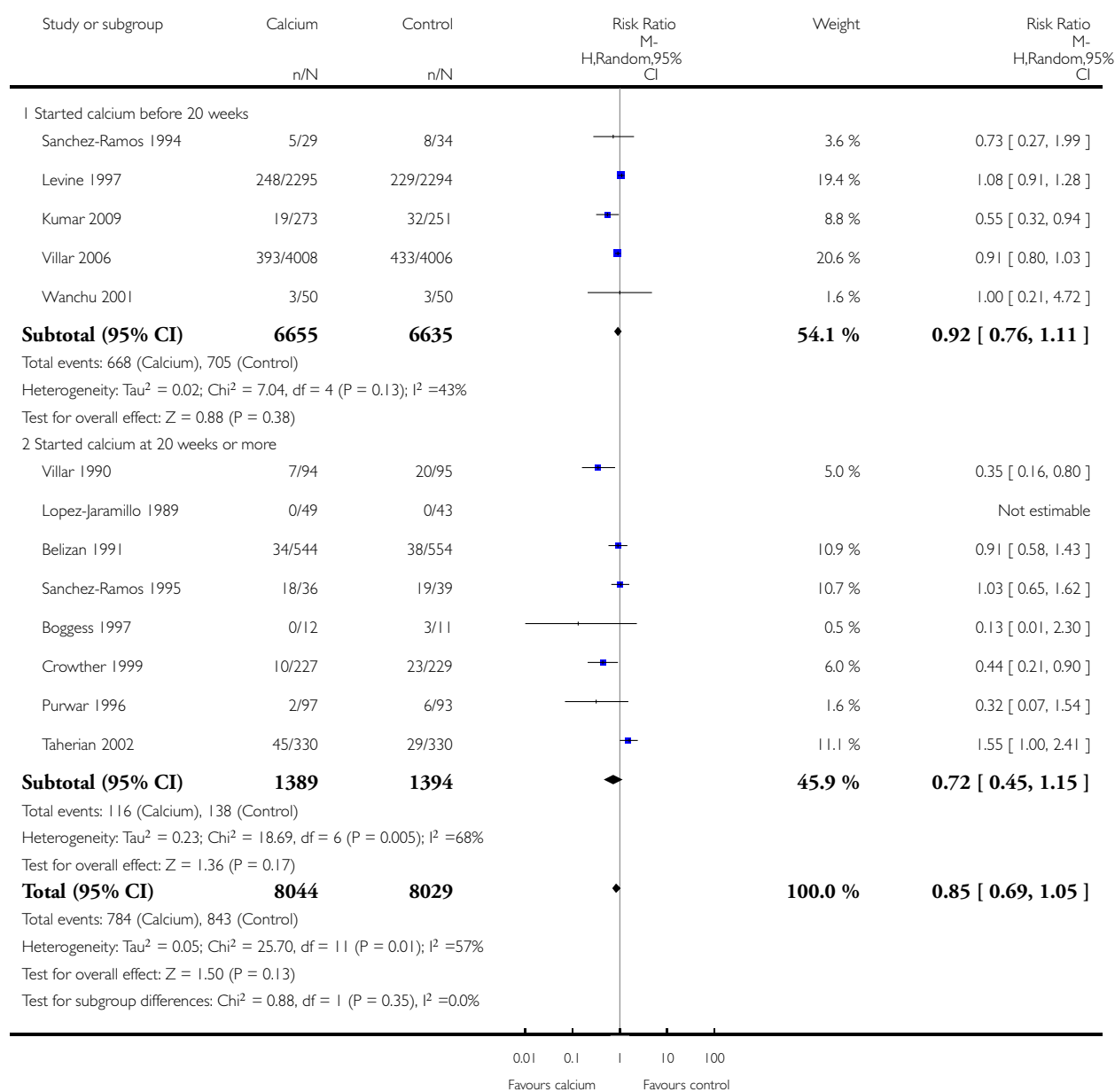


Analysis 1.3. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 3 Preterm birth (a) Birth prior to 37 weeks by started to take calcium.

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 1 Calcium supplementation versus placebo or no treatment (maternal outcomes)

Outcome: 3 Preterm birth (a) Birth prior to 37 weeks by started to take calcium

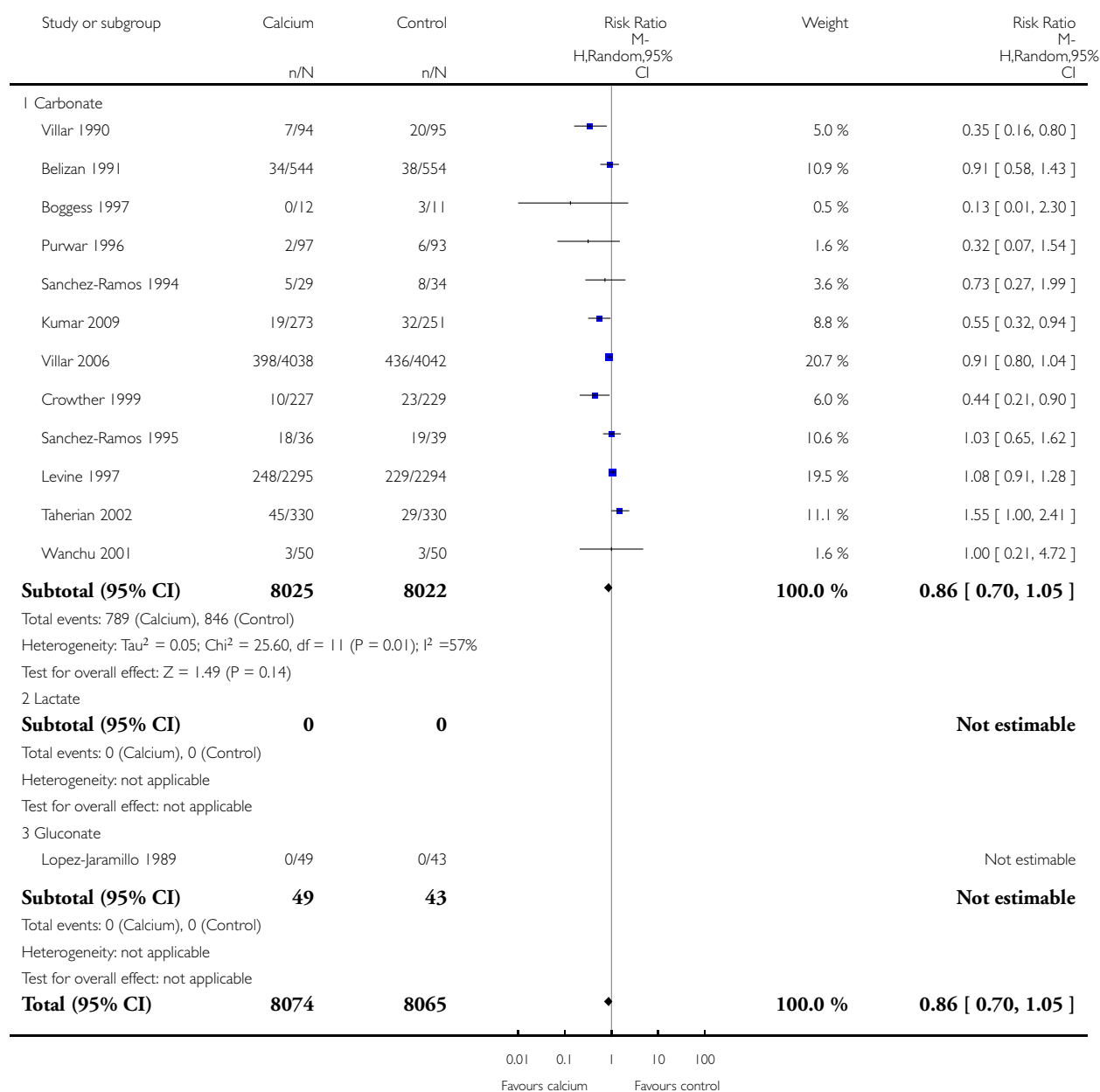


Analysis 1.4. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 4 Preterm birth (a) Birth prior to 37 weeks by type of calcium.

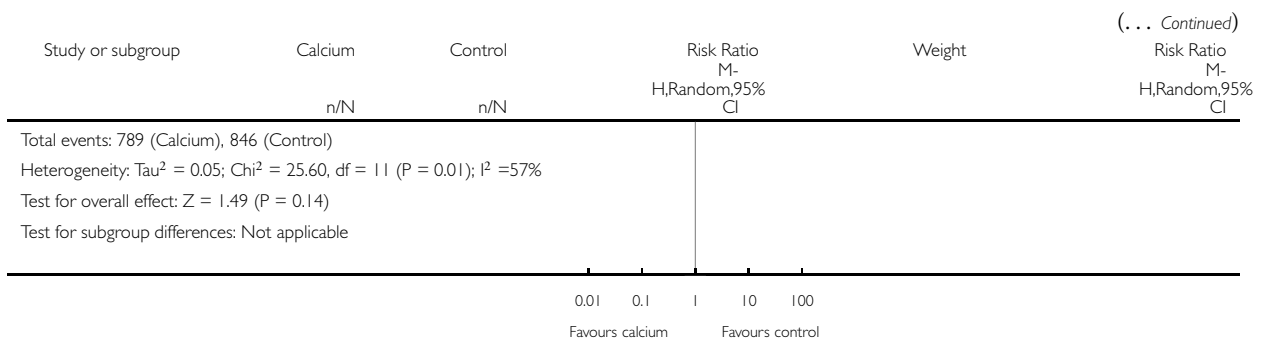
Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 1 Calcium supplementation versus placebo or no treatment (maternal outcomes)

Outcome: 4 Preterm birth (a) Birth prior to 37 weeks by type of calcium



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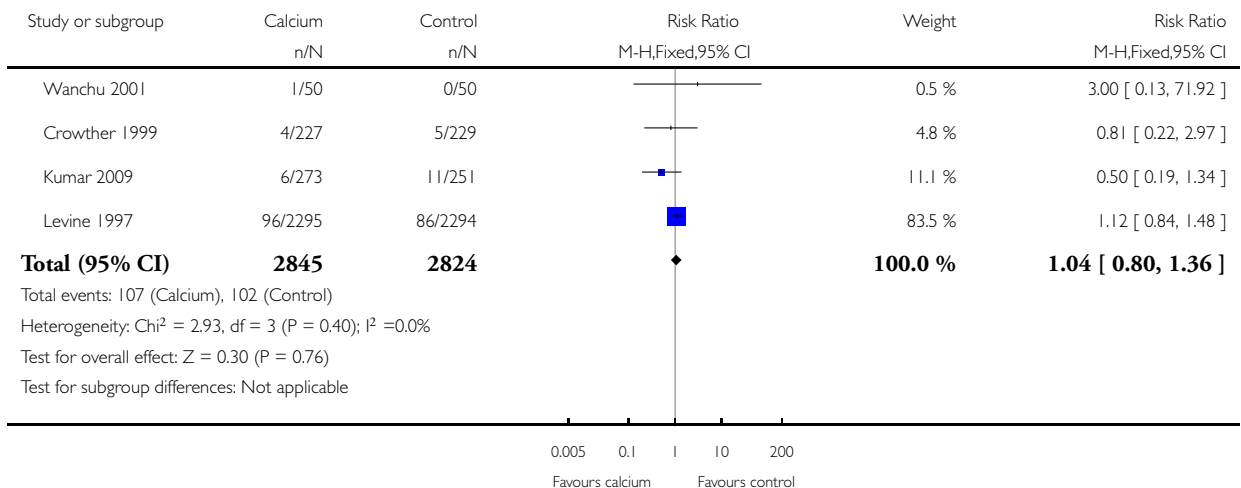


Analysis 1.5. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 5 Preterm birth (b) Birth prior to 34 weeks.

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 1 Calcium supplementation versus placebo or no treatment (maternal outcomes)

Outcome: 5 Preterm birth (b) Birth prior to 34 weeks

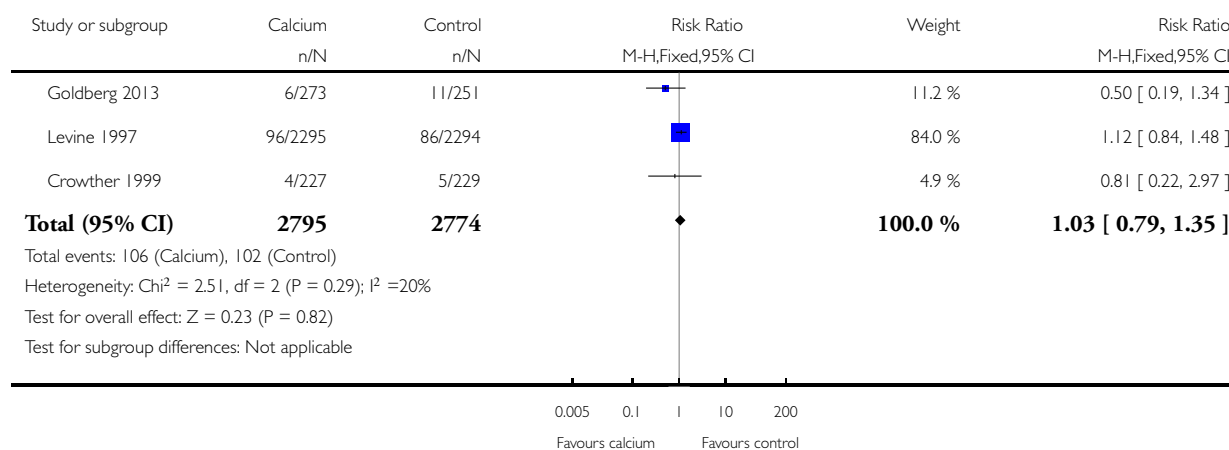


Analysis 1.6. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 6 Preterm birth (b) Birth prior to 34 weeks - Sensitivity analysis by concealment allocation.

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 1 Calcium supplementation versus placebo or no treatment (maternal outcomes)

Outcome: 6 Preterm birth (b) Birth prior to 34 weeks - Sensitivity analysis by concealment allocation

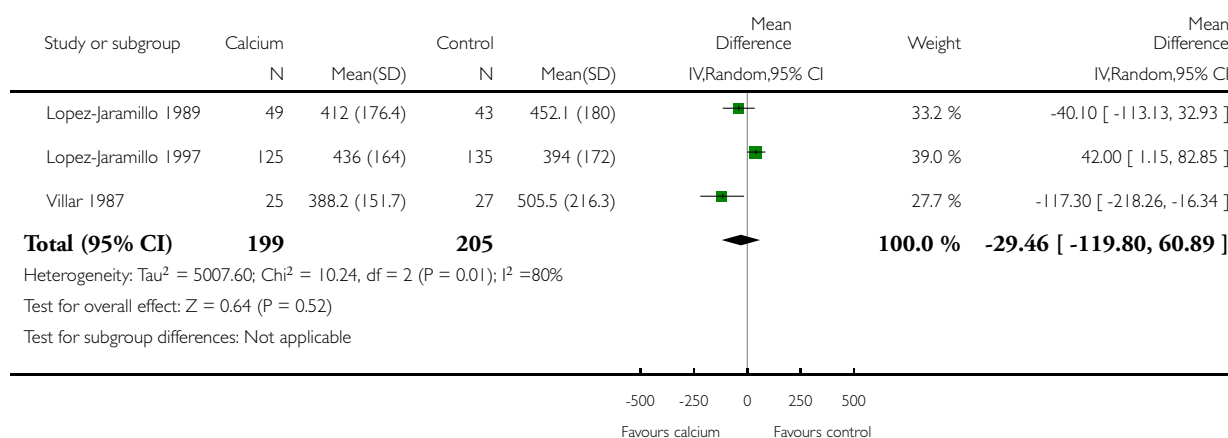


Analysis 1.7. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 7 Maternal weight gain (g/w).

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 1 Calcium supplementation versus placebo or no treatment (maternal outcomes)

Outcome: 7 Maternal weight gain (g/w)

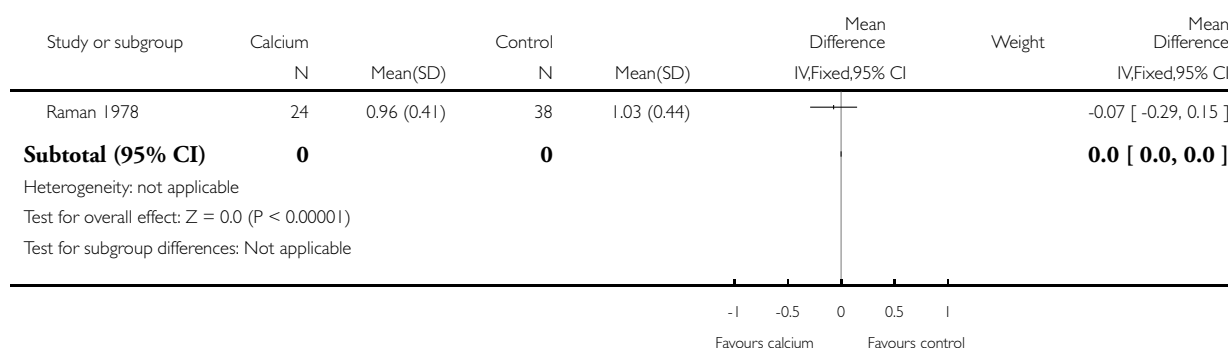


Analysis 1.8. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 8 Maternal bone mineral density (g/cm²) - First phalanx (calcium 300 mg).

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 1 Calcium supplementation versus placebo or no treatment (maternal outcomes)

Outcome: 8 Maternal bone mineral density (g/cm²) - First phalanx (calcium 300 mg)

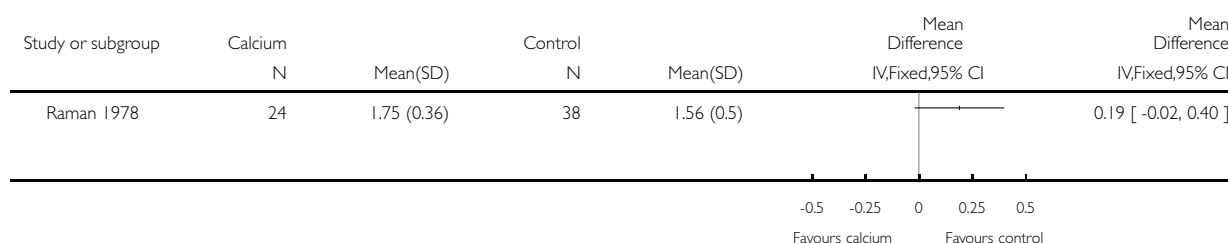


Analysis 1.9. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 9 Maternal bone mineral density (g/cm²) - Second metacarpal (calcium 300 mg).

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 1 Calcium supplementation versus placebo or no treatment (maternal outcomes)

Outcome: 9 Maternal bone mineral density (g/cm²) - Second metacarpal (calcium 300 mg)

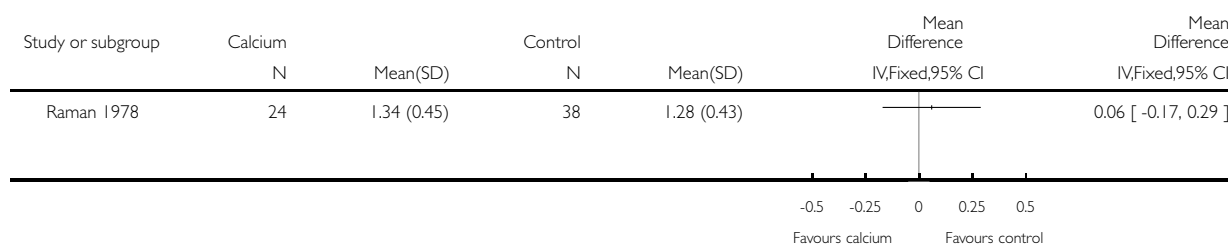


Analysis 1.10. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 10 Maternal bone mineral density (g/cm²) - Fourth metacarpal (calcium 300 mg).

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 1 Calcium supplementation versus placebo or no treatment (maternal outcomes)

Outcome: 10 Maternal bone mineral density (g/cm²) - Fourth metacarpal (calcium 300 mg)

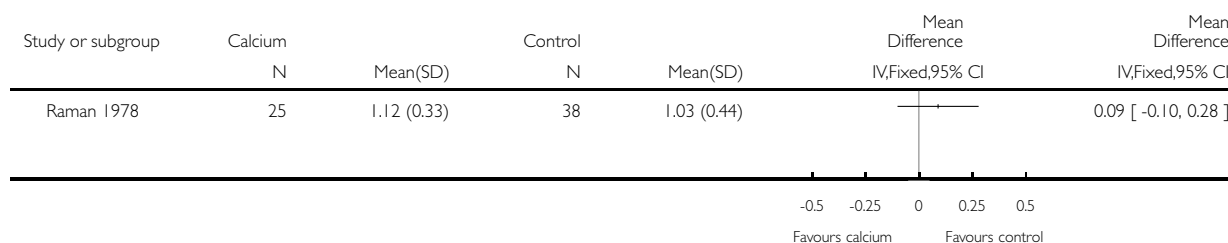


Analysis 1.11. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 11 Maternal bone mineral density (g/cm²) - First phalanx (calcium 600 mg).

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 1 Calcium supplementation versus placebo or no treatment (maternal outcomes)

Outcome: 11 Maternal bone mineral density (g/cm²) - First phalanx (calcium 600 mg)

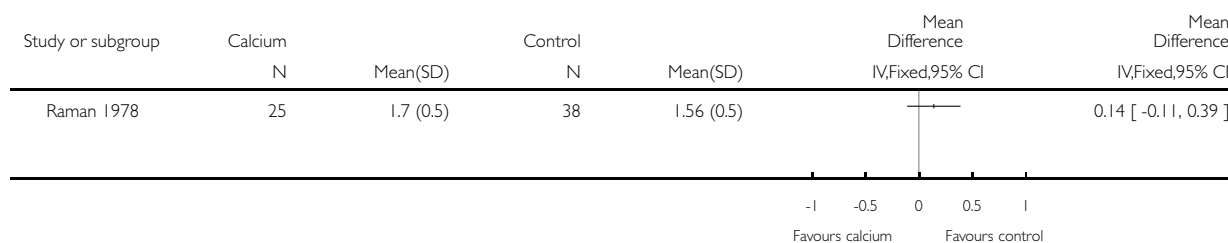


Analysis 1.12. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 12 Maternal bone mineral density (g/cm²) - Second metacarpal (calcium 600 mg).

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 1 Calcium supplementation versus placebo or no treatment (maternal outcomes)

Outcome: 12 Maternal bone mineral density (g/cm²) - Second metacarpal (calcium 600 mg)

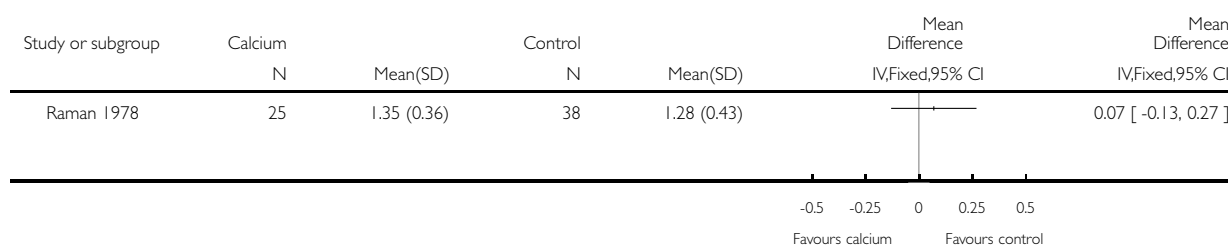


Analysis 1.13. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 13 Maternal bone mineral density (g/cm²) - Fourth metacarpal (calcium 600 mg).

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 1 Calcium supplementation versus placebo or no treatment (maternal outcomes)

Outcome: 13 Maternal bone mineral density (g/cm²) - Fourth metacarpal (calcium 600 mg)

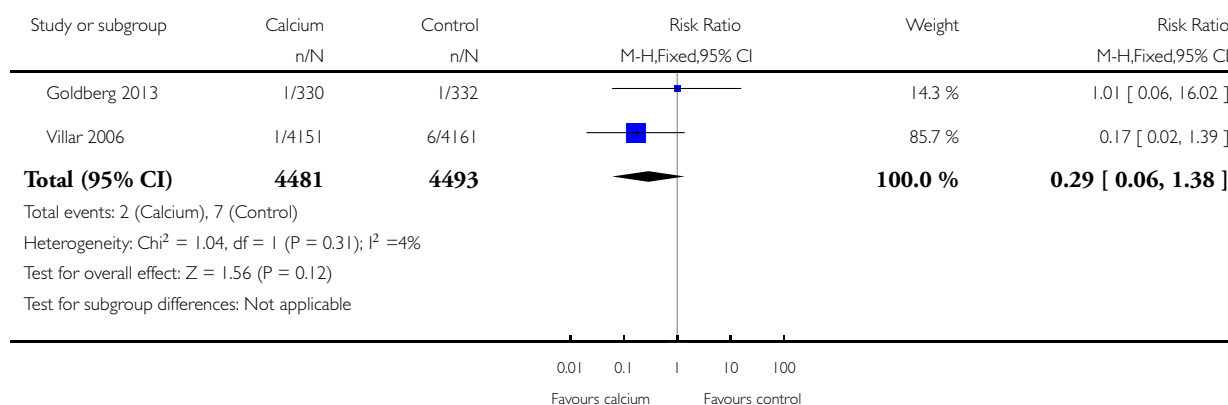


Analysis 1.14. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 14 Maternal death.

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 1 Calcium supplementation versus placebo or no treatment (maternal outcomes)

Outcome: 14 Maternal death

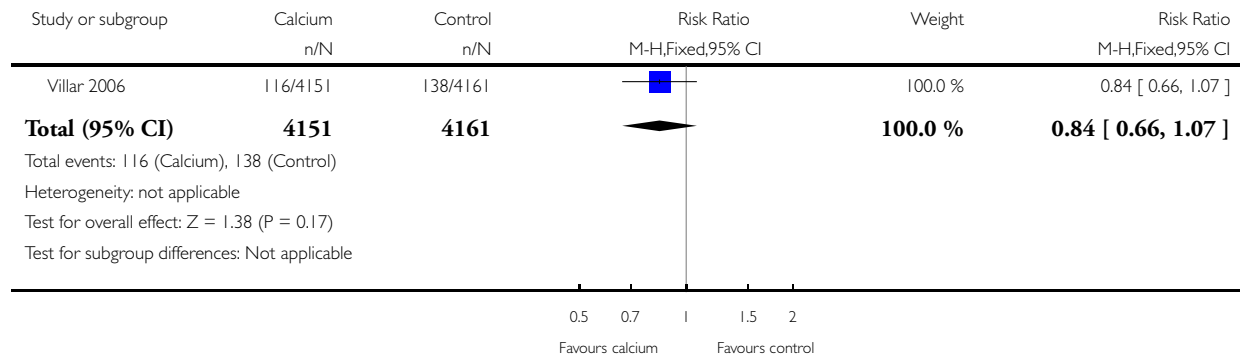


Analysis 1.15. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 15 Maternal admission to intensive care unit.

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 1 Calcium supplementation versus placebo or no treatment (maternal outcomes)

Outcome: 15 Maternal admission to intensive care unit

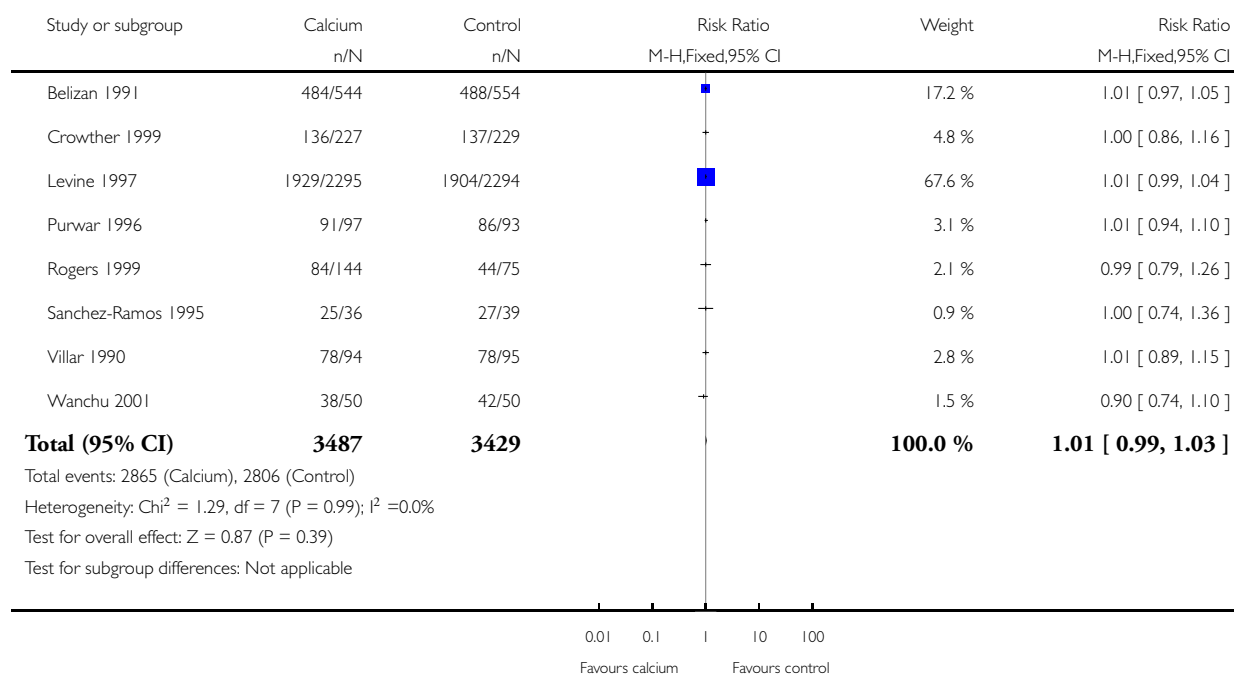


Analysis 1.16. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 16 Vaginal birth.

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 1 Calcium supplementation versus placebo or no treatment (maternal outcomes)

Outcome: 16 Vaginal birth

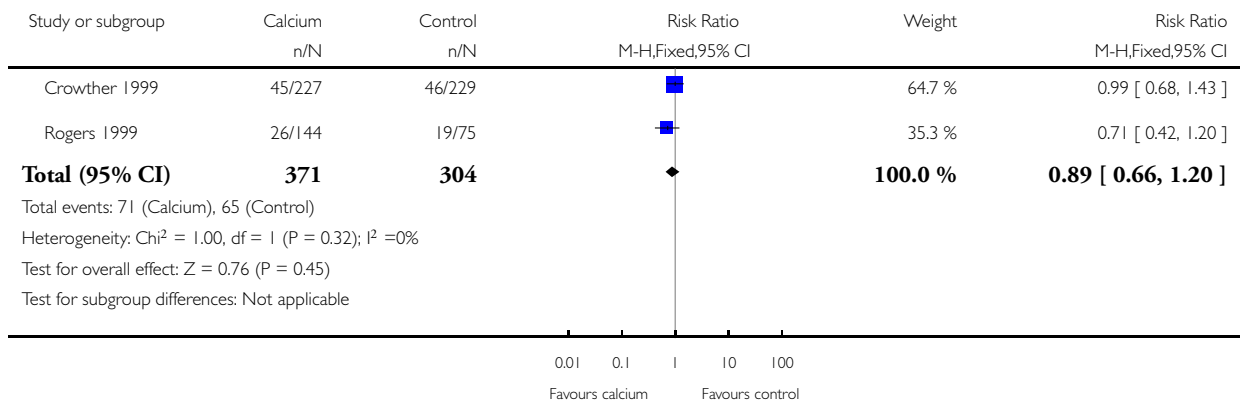


Analysis 1.17. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 17 Instrumental vaginal birth.

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 1 Calcium supplementation versus placebo or no treatment (maternal outcomes)

Outcome: 17 Instrumental vaginal birth

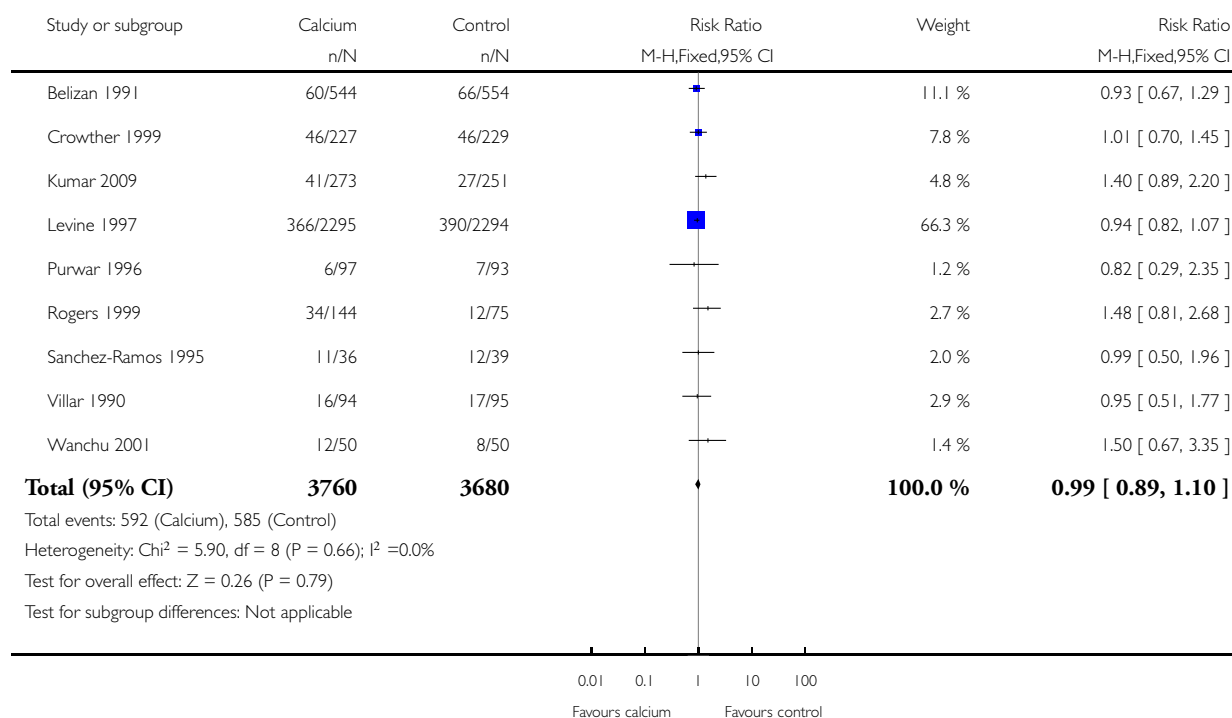


Analysis 1.18. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 18 Caesarean section.

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 1 Calcium supplementation versus placebo or no treatment (maternal outcomes)

Outcome: 18 Caesarean section

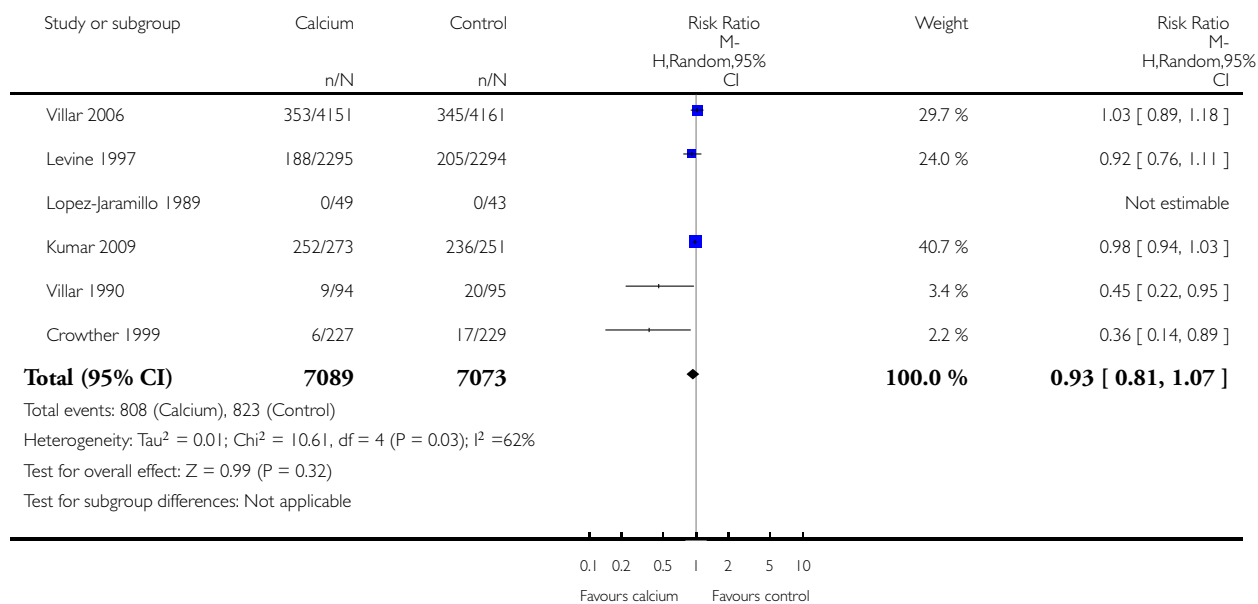


Analysis 2.1. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 1 Low birthweight (< 2500 g).

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 2 Calcium supplementation versus placebo or no treatment (infant outcomes)

Outcome: 1 Low birthweight (< 2500 g)

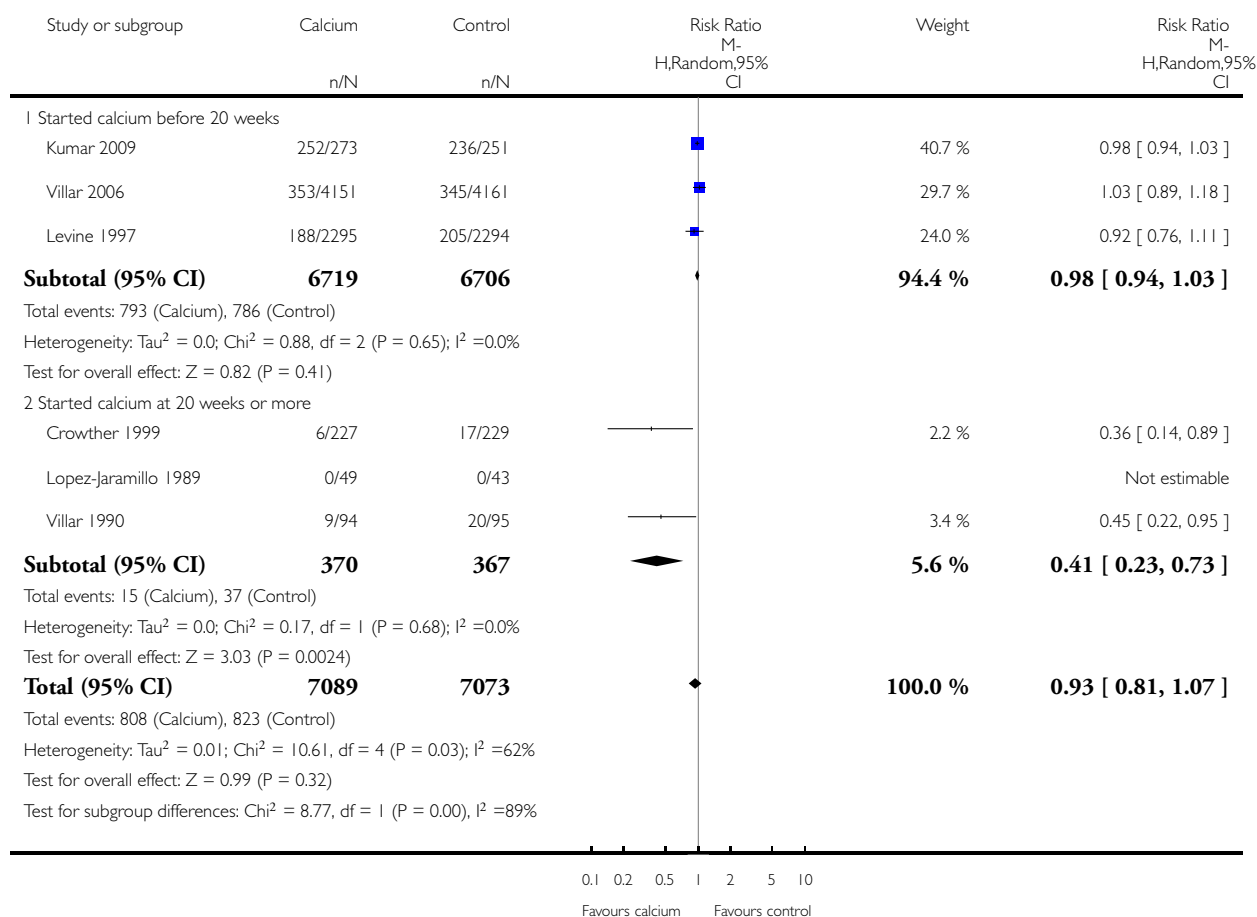


Analysis 2.2. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 2 Low birthweight (< 2500 g) by started to take calcium.

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 2 Calcium supplementation versus placebo or no treatment (infant outcomes)

Outcome: 2 Low birthweight (< 2500 g) by started to take calcium

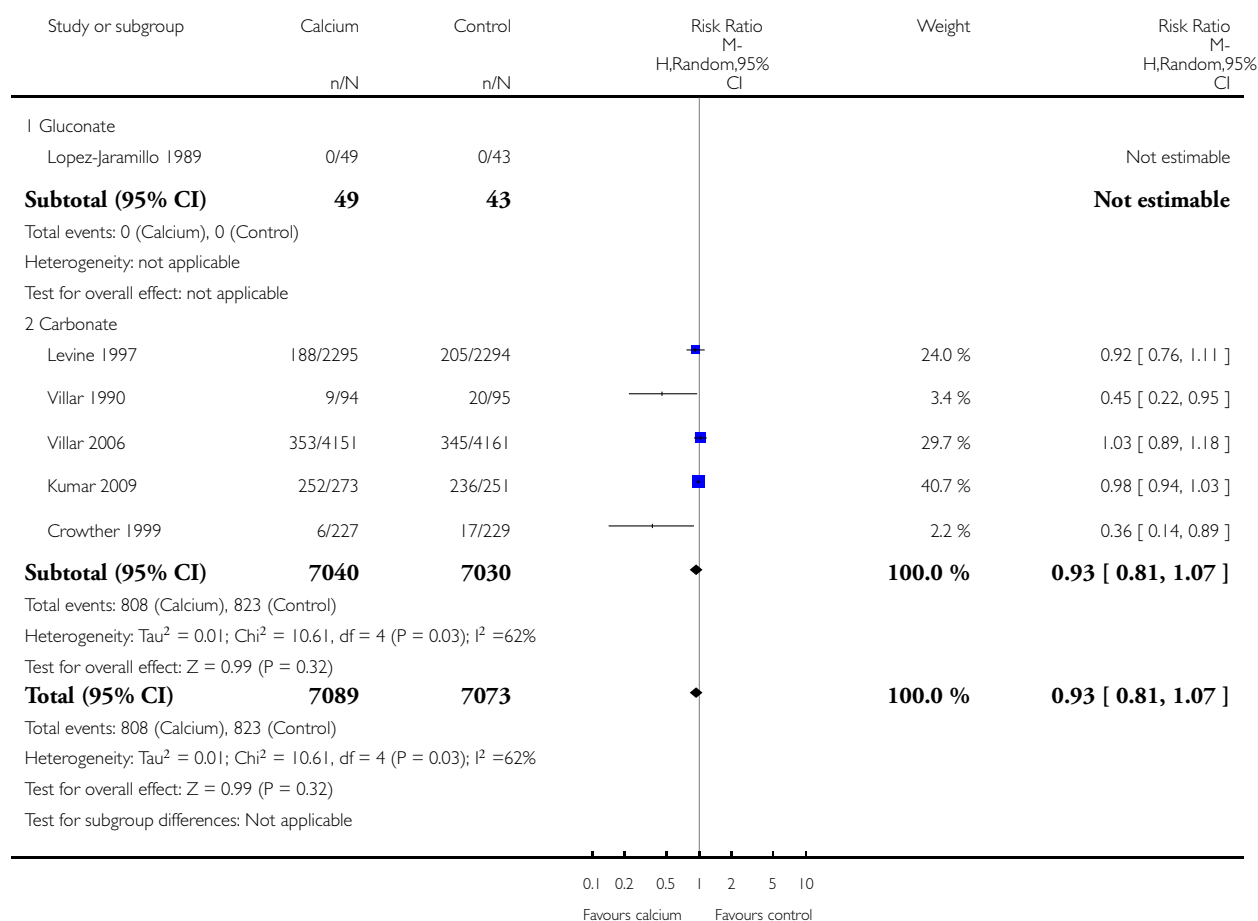


Analysis 2.3. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 3 Low birthweight (< 2500 g) by type of calcium.

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 2 Calcium supplementation versus placebo or no treatment (infant outcomes)

Outcome: 3 Low birthweight (< 2500 g) by type of calcium

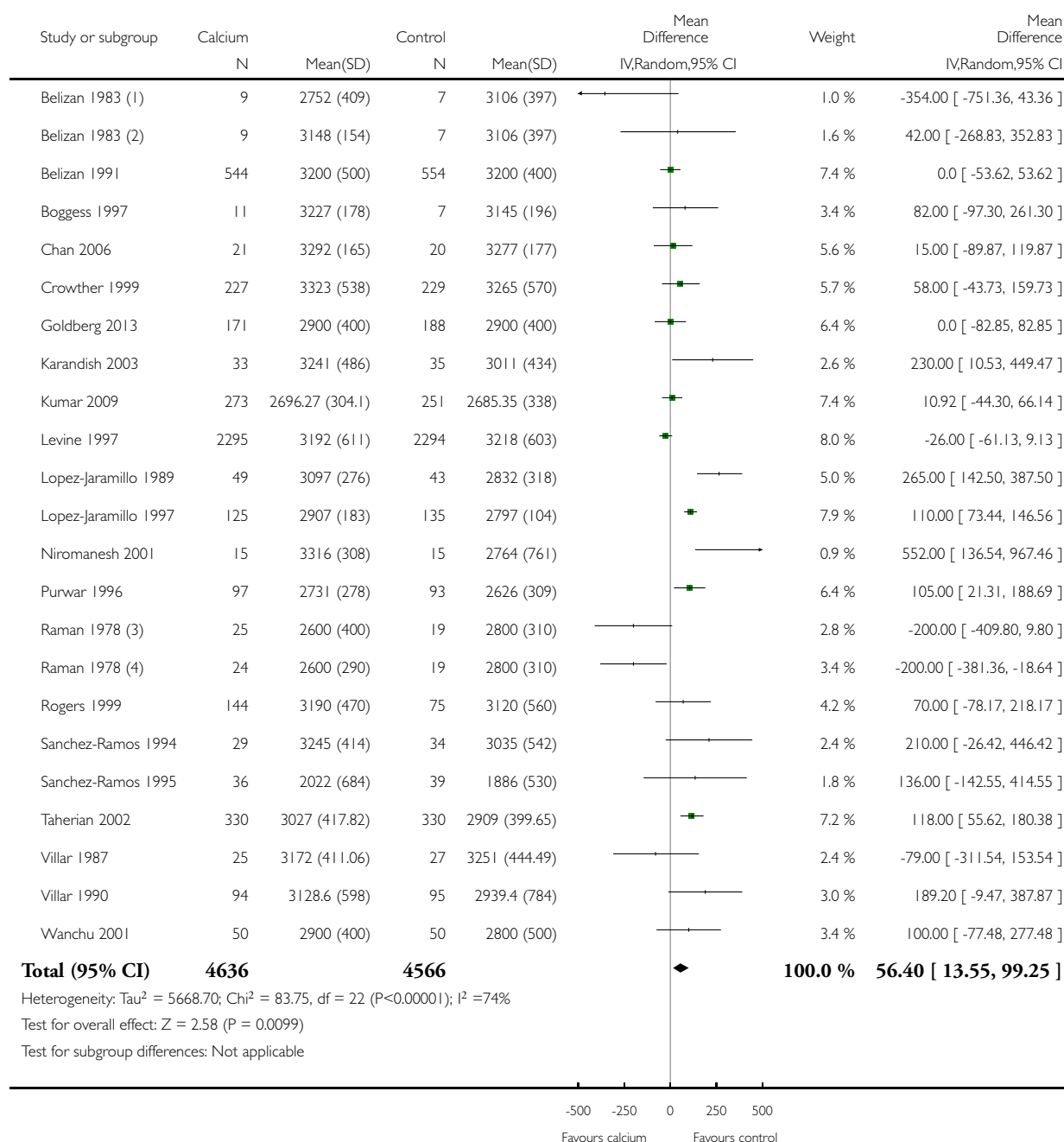


Analysis 2.4. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 4 Birthweight (g).

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 2 Calcium supplementation versus placebo or no treatment (infant outcomes)

Outcome: 4 Birthweight (g)



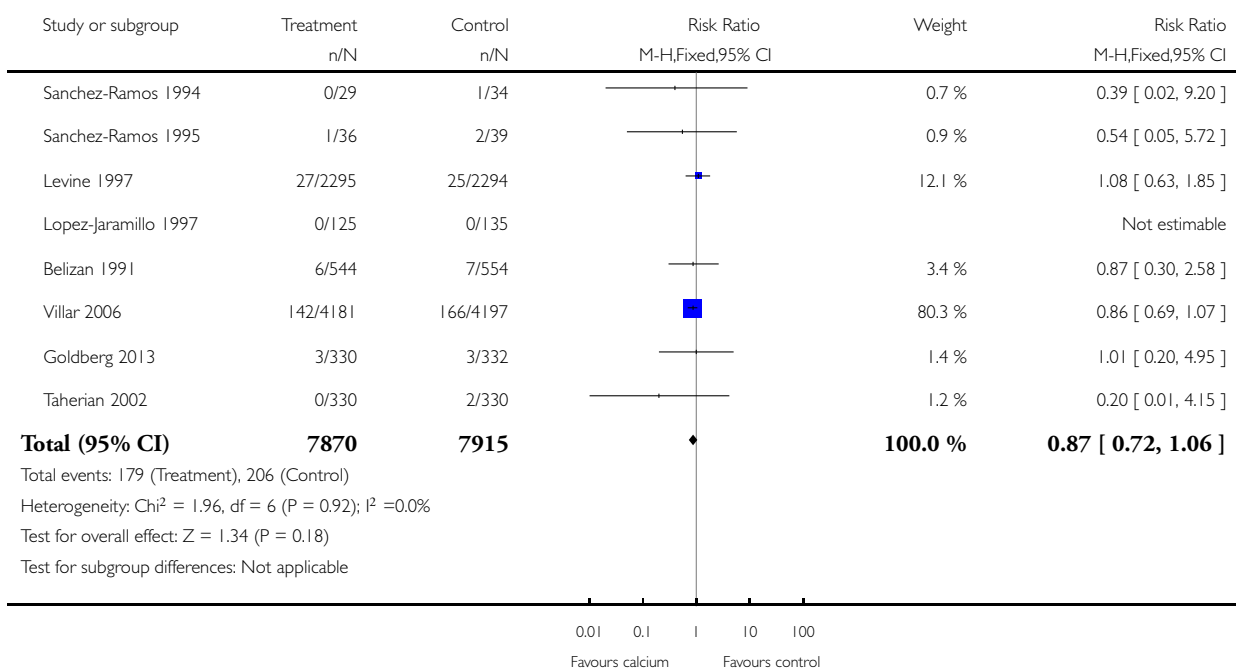
- (1) The treatment group received 1gm calcium per day
- (2) The treatment group received 2gm calcium per day
- (3) The treatment group received 600mg calcium per day
- (4) The treatment group received 300mg calcium per day

Analysis 2.5. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 5 Perinatal mortality.

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 2 Calcium supplementation versus placebo or no treatment (infant outcomes)

Outcome: 5 Perinatal mortality

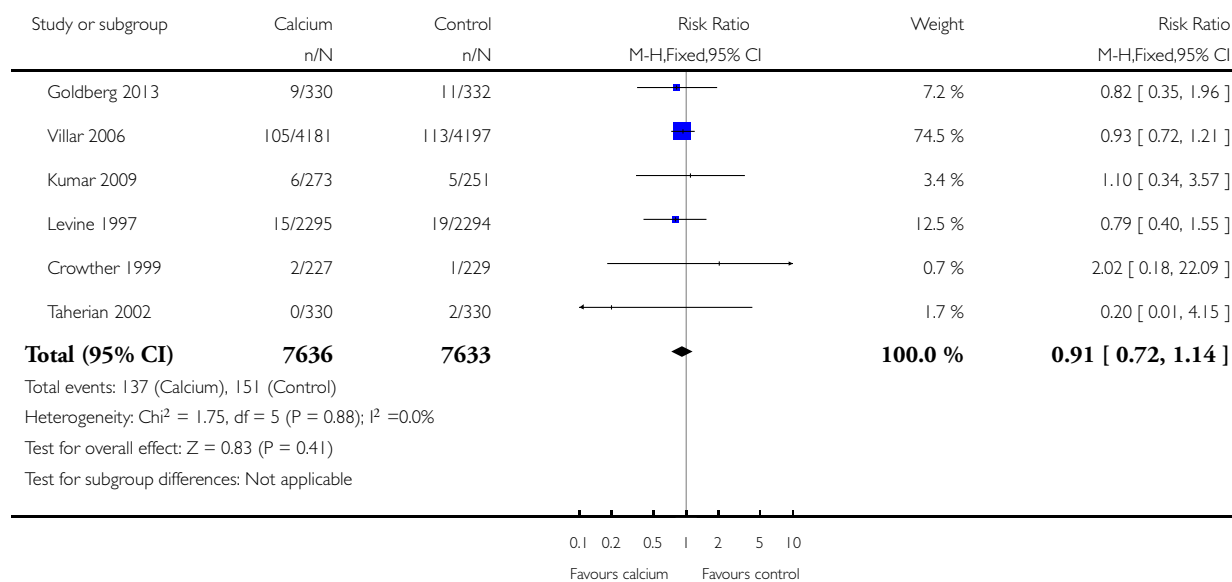


Analysis 2.6. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 6 Stillbirth or fetal death.

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 2 Calcium supplementation versus placebo or no treatment (infant outcomes)

Outcome: 6 Stillbirth or fetal death

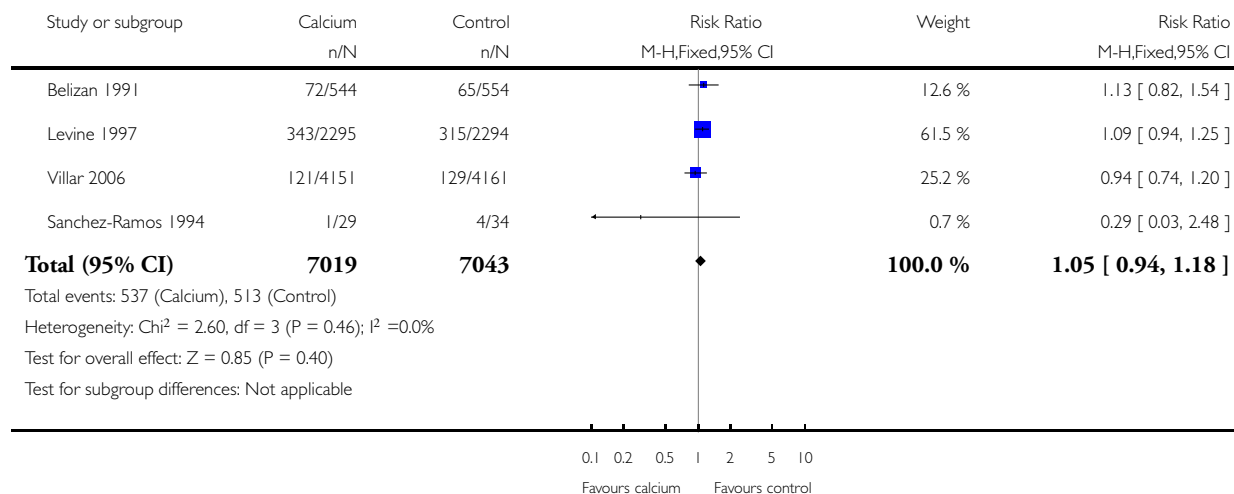


Analysis 2.7. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 7 Admission to neonatal intensive care unit.

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 2 Calcium supplementation versus placebo or no treatment (infant outcomes)

Outcome: 7 Admission to neonatal intensive care unit

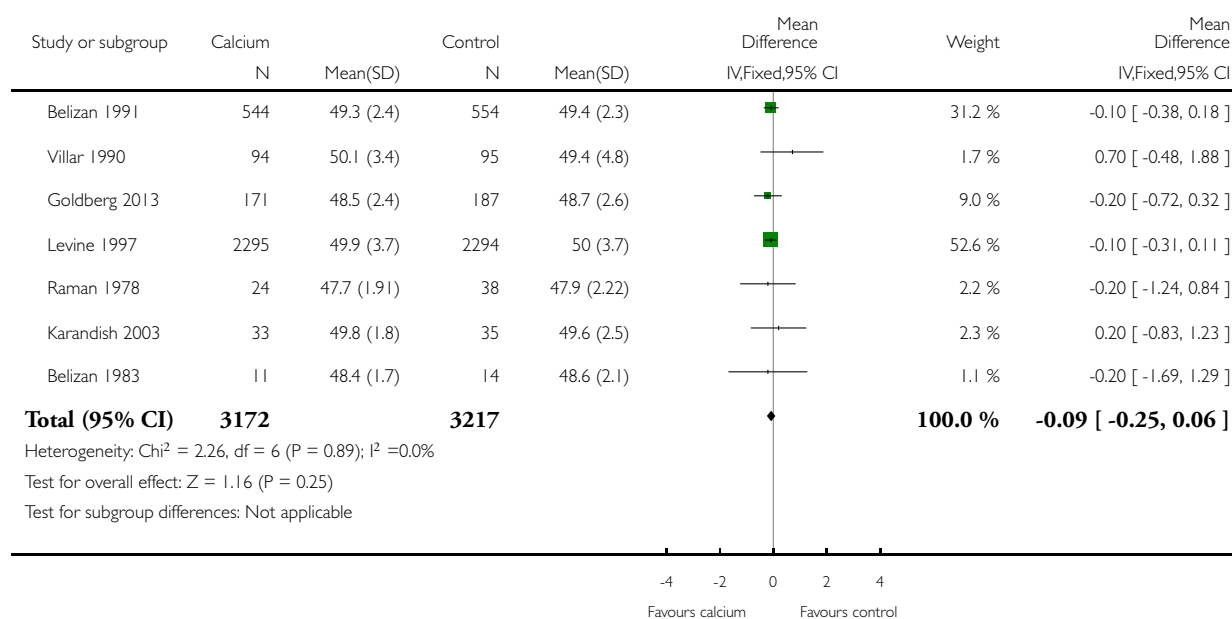


Analysis 2.8. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 8 Birth length (cm).

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 2 Calcium supplementation versus placebo or no treatment (infant outcomes)

Outcome: 8 Birth length (cm)

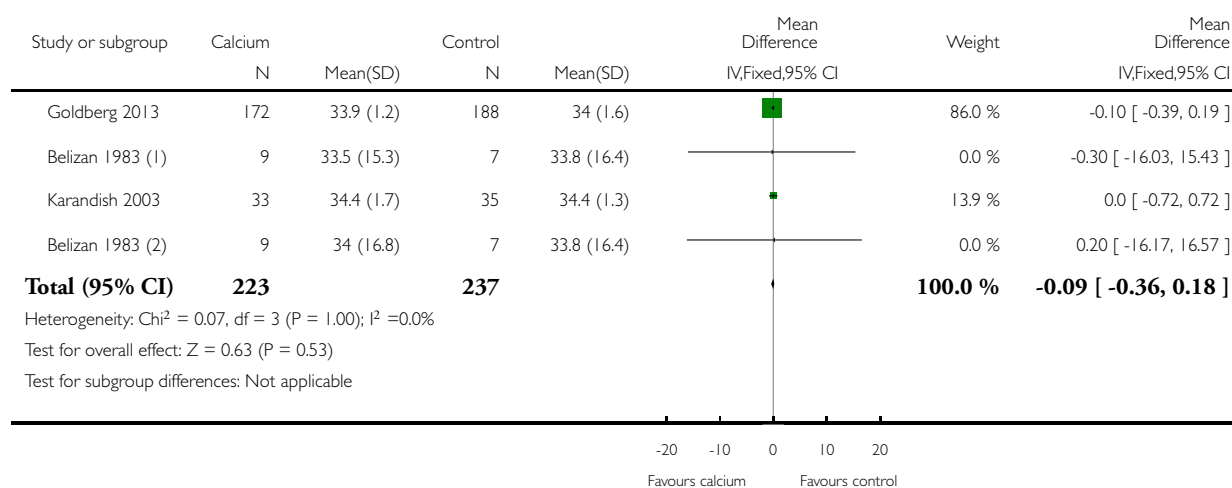


Analysis 2.9. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 9 Head circumference (cm).

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 2 Calcium supplementation versus placebo or no treatment (infant outcomes)

Outcome: 9 Head circumference (cm)



(1) Treatment group received 1gm calcium per day

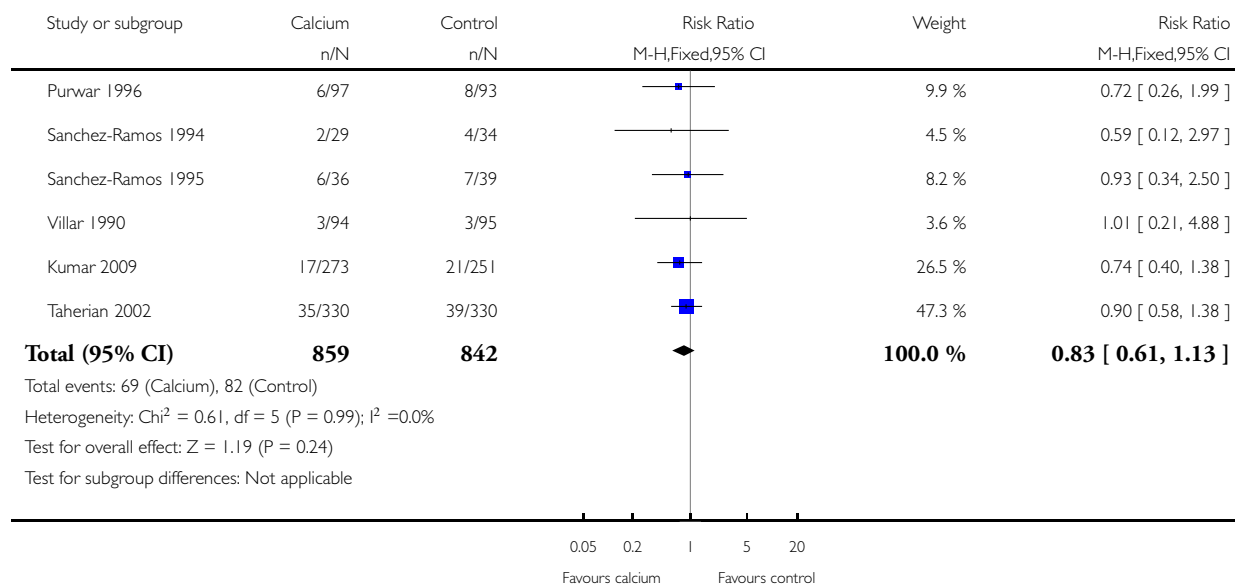
(2) Treatment group received 2gm calcium per day

Analysis 2.10. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 10 Intrauterine growth restriction.

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 2 Calcium supplementation versus placebo or no treatment (infant outcomes)

Outcome: 10 Intrauterine growth restriction

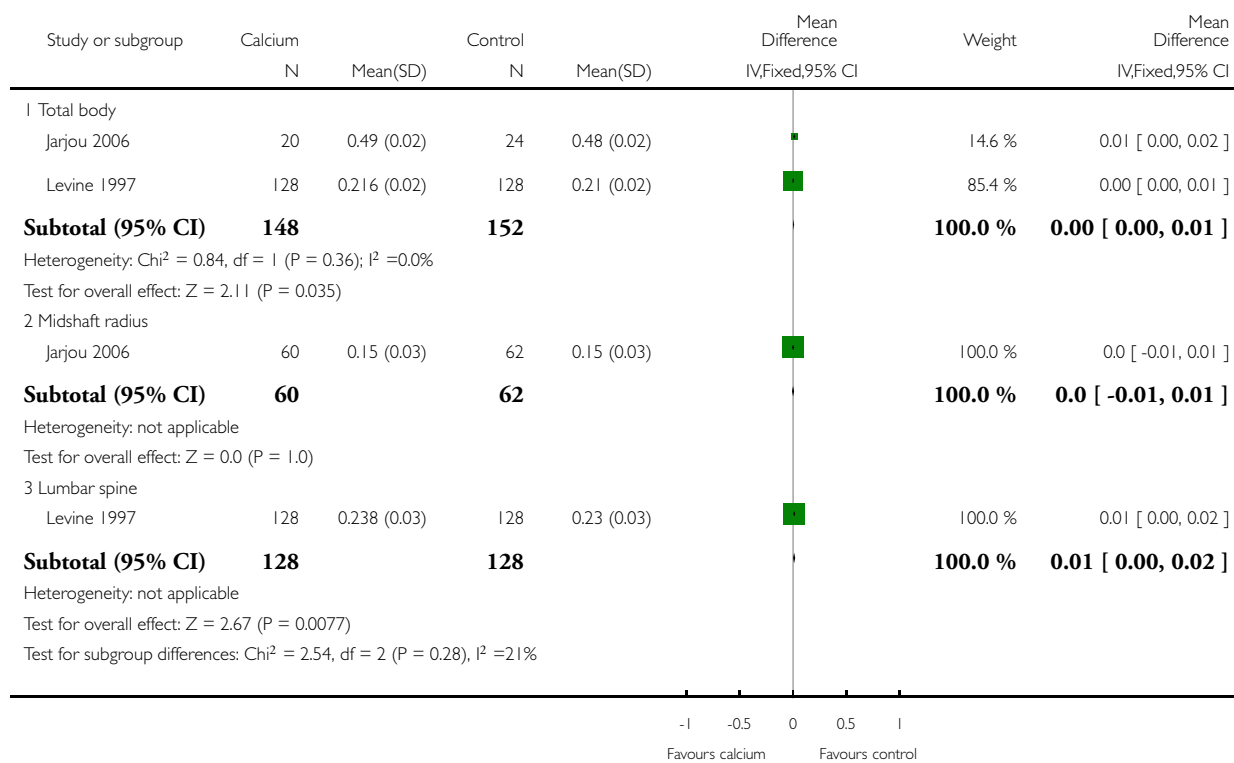


Analysis 2.11. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 11 Neonatal bone mineral density (g/cm²).

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 2 Calcium supplementation versus placebo or no treatment (infant outcomes)

Outcome: 11 Neonatal bone mineral density (g/cm²)

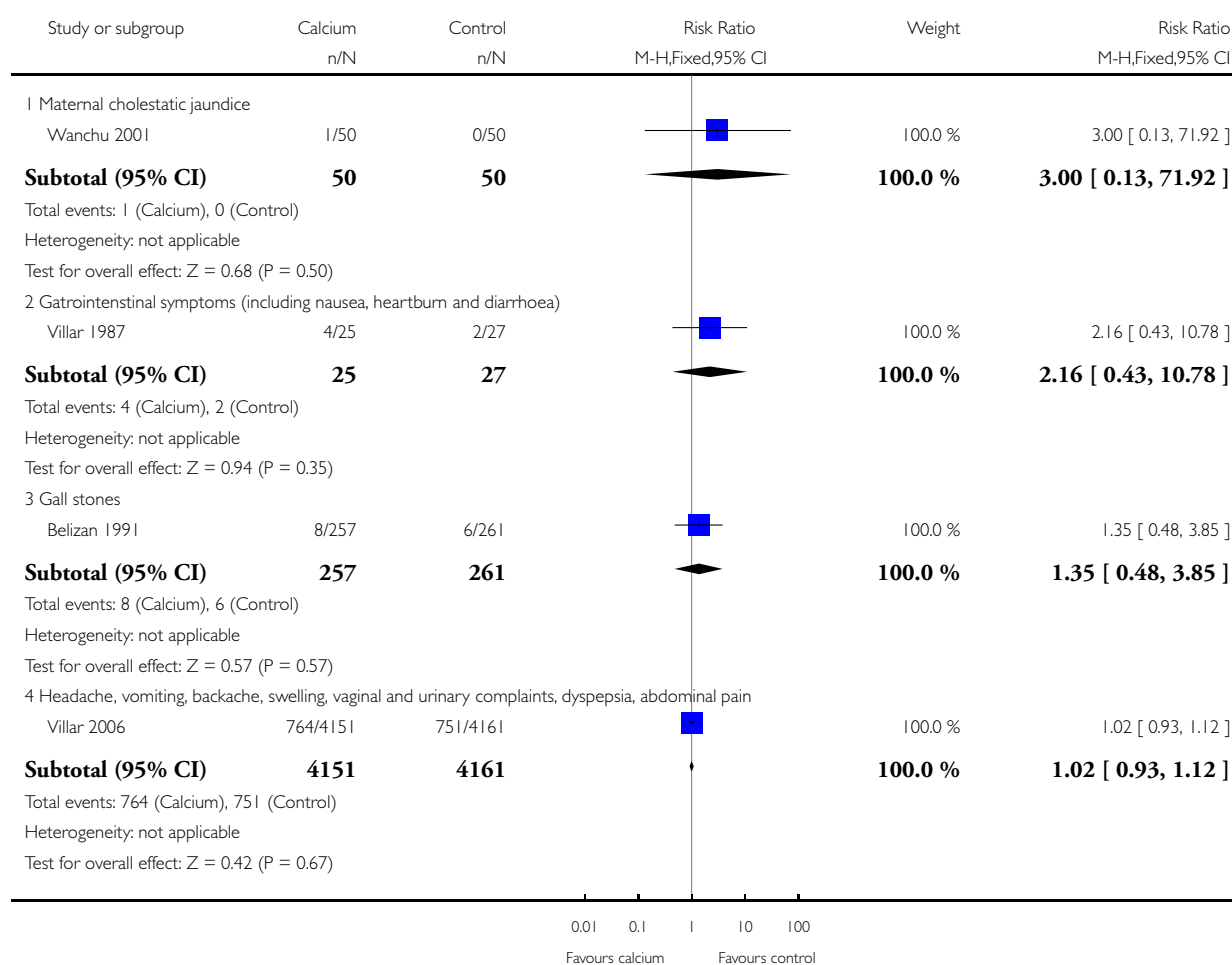


Analysis 3.1. Comparison 3 Calcium supplementation versus placebo or no treatment (adverse outcomes), Outcome 1 Side effects of calcium supplementation - Maternal cholestatic jaundice.

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 3 Calcium supplementation versus placebo or no treatment (adverse outcomes)

Outcome: 1 Side effects of calcium supplementation - Maternal cholestatic jaundice

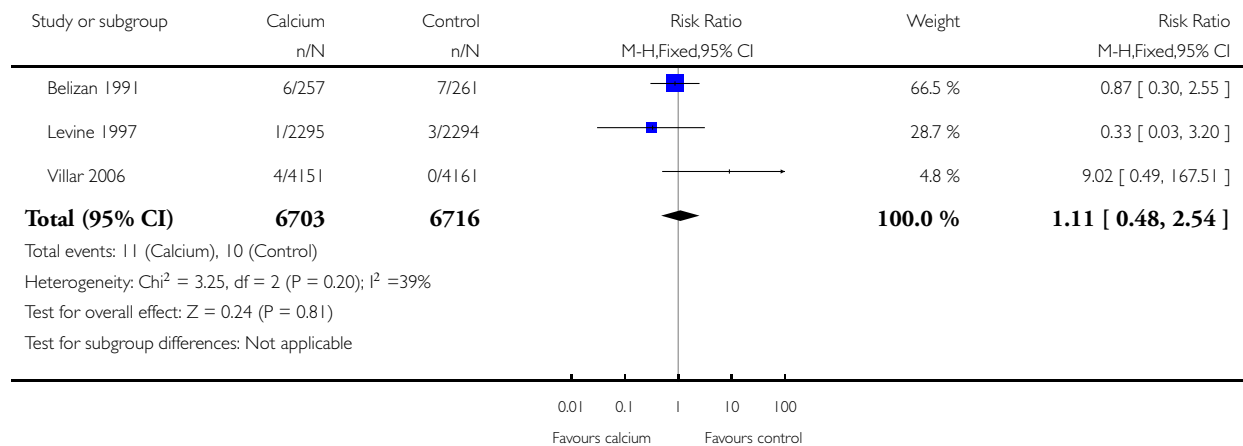


Analysis 3.2. Comparison 3 Calcium supplementation versus placebo or no treatment (adverse outcomes), Outcome 2 Urinary stones.

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 3 Calcium supplementation versus placebo or no treatment (adverse outcomes)

Outcome: 2 Urinary stones

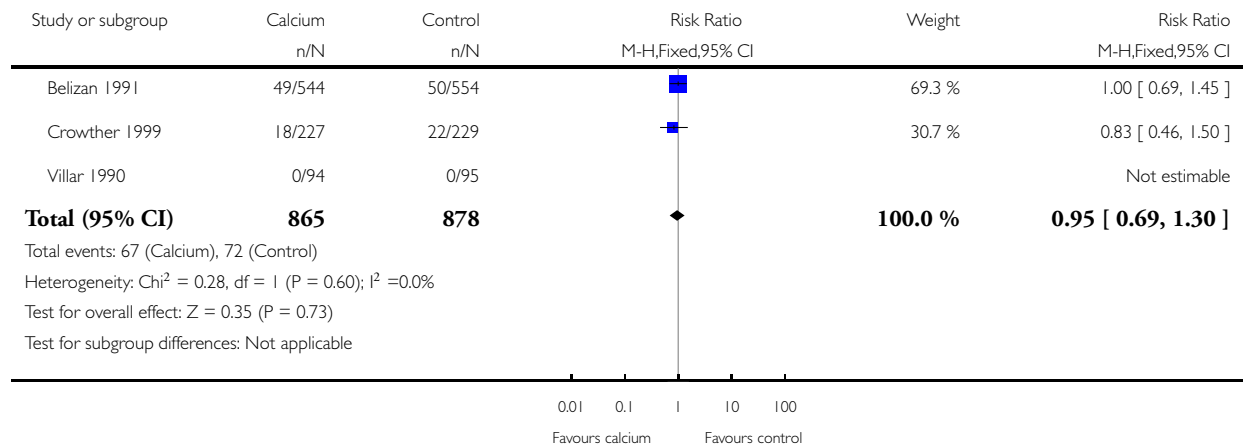


Analysis 3.3. Comparison 3 Calcium supplementation versus placebo or no treatment (adverse outcomes), Outcome 3 Urinary tract infection.

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 3 Calcium supplementation versus placebo or no treatment (adverse outcomes)

Outcome: 3 Urinary tract infection

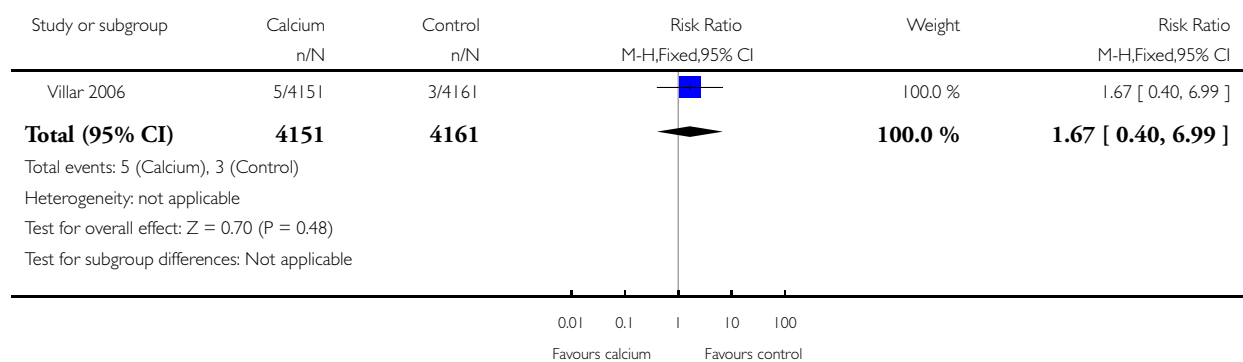


Analysis 3.4. Comparison 3 Calcium supplementation versus placebo or no treatment (adverse outcomes), Outcome 4 Renal colic.

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 3 Calcium supplementation versus placebo or no treatment (adverse outcomes)

Outcome: 4 Renal colic

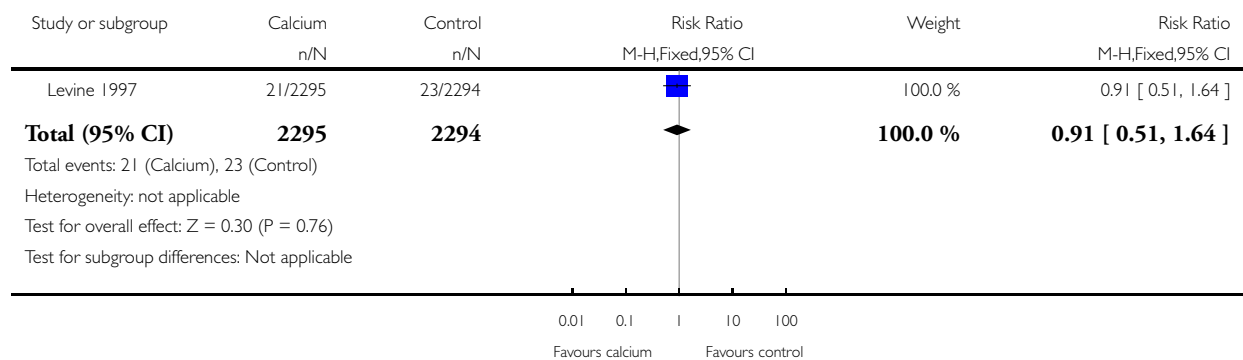


Analysis 3.5. Comparison 3 Calcium supplementation versus placebo or no treatment (adverse outcomes), Outcome 5 Impaired renal function.

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 3 Calcium supplementation versus placebo or no treatment (adverse outcomes)

Outcome: 5 Impaired renal function

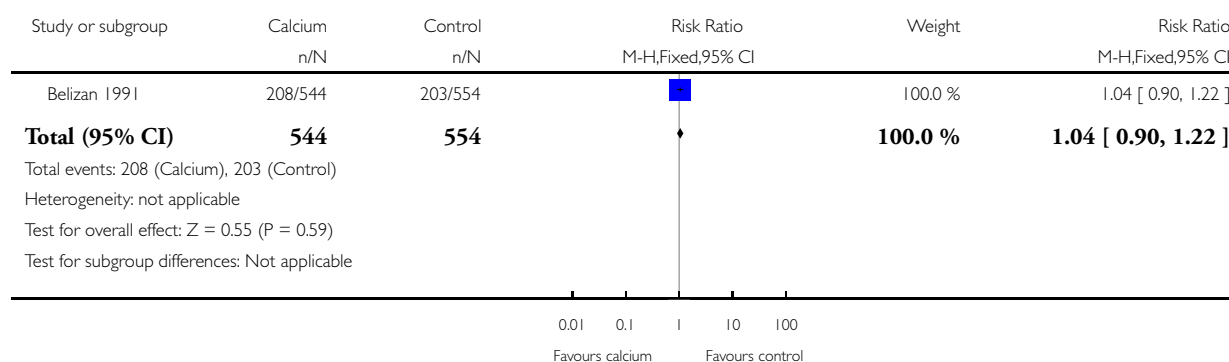


Analysis 3.6. Comparison 3 Calcium supplementation versus placebo or no treatment (adverse outcomes), Outcome 6 Maternal anemia.

Review: Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: 3 Calcium supplementation versus placebo or no treatment (adverse outcomes)

Outcome: 6 Maternal anemia



ADDITIONAL TABLES

Table 1. Neonatal bone density (Skewed data)

Study	Outcome	Treatment			Control		
		Mean	SD	Total	Mean	SD	Total
Raman 1978 (Ca 300 mg)	Ulna	1.19	0.81	24	0.64	0.26	38
Raman 1978 (Ca 300 mg)	Fibula	1.12	0.6	24	0.65	0.41	38
Raman 1978 (Ca 300 mg)	Midshaft radius	1.17	0.62	24	0.08	0.4	38
Raman 1978 (Ca 300 mg)	Tibia	0.91	0.35	24	0.58	0.41	38
Raman 1978 (Ca 600 mg)	Ulna	1.03	0.53	25	0.64	0.26	38
Raman 1978 (Ca 600 mg)	Midshaft radius	1.17	0.65	25	0.08	0.4	38

Table 1. Neonatal bone density (Skewed data) (Continued)

Raman 1978 (Ca 600 mg)	Tibia	1.11	0.82	25	0.58	0.41	38
Raman 1978 (Ca 600 mg)	Fibula	1.51	0.61	25	0.65	0.41	38

The standard deviation (SD) was imputed from the standard error of a mean (SEM).

WHAT'S NEW

Last assessed as up-to-date: 30 September 2014.

Date	Event	Description
30 September 2014	New citation required but conclusions have not changed	Review updated.
30 September 2014	New search has been performed	Search updated and 19 new reports were assessed for eligibility. Three new trials were included (Goldberg 2013 ; Herrera 2006 ; Kumar 2009). Four reports were abstracts added to awaiting classification, one of which requires translation (Zheng 2000). Six reports were duplicates for already included studies. Six reports were excluded. Methods updated and 'Summary of findings' table added

CONTRIBUTIONS OF AUTHORS

P Buppasiri (PB) developed the protocol. P Lumbiganon (PL) and J Thinkhamrop (JT) edited and commented on the protocol. C Ngamjarus (CN) commented on the protocol.

For the review, PB and JT independently extracted the data. CN conducted the statistical analysis and summarised the results. PB drafted the review. All review authors commented and finalised the review.

For the updated review, PB and Nancy Medley (NM) independently extracted new data and updated the review. NM added GRADE summary. All review authors commented and finalised the update review.

DECLARATIONS OF INTEREST

Malinee Laopaiboon received an honorarium from the Thailand Research Fund which is a non-profit organisation.

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Internal sources

- Faculty of Medicine, Khon Kaen University, Thailand.
- Faculty of Public Health, Khon Kaen University, Thailand.

External sources

- Thailand Research Fund / Senior Research Scholar, Thailand.
- SEA-ORCHID Project, Thailand.
- Department of Nutrition for Health and Development, WHO, Switzerland.
- UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research (RHR), World Health Organization, Switzerland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. We used stillbirth or fetal death as the same outcome, these were listed as separate outcomes in the protocol.
2. We added mode of birth (vaginal birth, instrumental birth, caesarean section), postpartum haemorrhage as secondary maternal outcomes.
3. We deleted limb pain from the list of neonatal outcomes and osteopenia and osteoporosis from the list of maternal outcomes.
4. We have modified the wording in the methods sections for [Assessment of risk of bias in included studies](#) and [Assessment of reporting biases](#) to update them with the current methods being used by the Cochrane Pregnancy and Childbirth Group. The quality of the evidence was assessed using the GRADE approach ([Schunemann 2009](#)) in order to assess the quality of the body of evidence relating key outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements [adverse effects]; *Infant, Low Birth Weight; *Pregnancy Outcome; *Prenatal Nutritional Physiological Phenomena; Birth Weight; Calcium, Dietary [*administration & dosage; adverse effects]; Pre-Eclampsia [prevention & control]; Premature Birth [*prevention & control]; Randomized Controlled Trials as Topic; Sensitivity and Specificity

MeSH check words

Female; Humans; Infant, Newborn; Pregnancy



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Antibiotic prophylaxis for third- and fourth-degree perineal tear during vaginal birth (Review)

Buppasiri P, Lumbiganon P, Thinkhamrop J, Thinkhamrop B

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Antibiotic prophylaxis for third- and fourth-degree perineal tear during vaginal birth.

Cochrane Database of Systematic Reviews 2014, Issue 10. Art. No.: CD005125.

DOI: 10.1002/14651858.CD005125.pub4.

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	3
BACKGROUND	5
OBJECTIVES	5
METHODS	5
RESULTS	8
Figure 1.	9
DISCUSSION	10
AUTHORS' CONCLUSIONS	10
ACKNOWLEDGEMENTS	10
REFERENCES	11
CHARACTERISTICS OF STUDIES	13
DATA AND ANALYSES	16
Analysis 1.1. Comparison 1 Antibiotic prophylaxis versus no treatment for perineal tear, Outcome 1 Infection rate at 2 weeks postpartum.	17
Analysis 1.2. Comparison 1 Antibiotic prophylaxis versus no treatment for perineal tear, Outcome 2 Infection rate at 6 weeks postpartum.	18
APPENDICES	18
WHAT'S NEW	23
HISTORY	23
CONTRIBUTIONS OF AUTHORS	23
DECLARATIONS OF INTEREST	23
SOURCES OF SUPPORT	24
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	24
NOTES	24
INDEX TERMS	24

[Intervention Review]

Antibiotic prophylaxis for third- and fourth-degree perineal tear during vaginal birth

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Editorial group: Cochrane Pregnancy and Childbirth Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 10, 2014.

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ABSTRACT

Background

One to eight per cent of women suffer third-degree perineal tear (anal sphincter injury) and fourth-degree perineal tear (rectal mucosa injury) during vaginal birth, and these tears are more common after forceps delivery (28%) and midline episiotomies. Third- and fourth-degree tears can become contaminated with bacteria from the rectum and this significantly increases in the chance of perineal wound infection. Prophylactic antibiotics might have a role in preventing this infection.

Objectives

To assess the effectiveness of antibiotic prophylaxis for reducing maternal morbidity and side effects in third- and fourth-degree perineal tear during vaginal birth.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 August 2014) and the reference lists of retrieved articles.

Selection criteria

Randomised controlled trials comparing outcomes of prophylactic antibiotics versus placebo or no antibiotics in third- and fourth-degree perineal tear during vaginal birth.

Data collection and analysis

Two review authors independently assessed the trial reports for inclusion and risk of bias, extracted data and checked them for accuracy.

Main results

We identified and included one trial (147 women from a pre-planned sample size of 310 women) that compared the effect of prophylactic antibiotic (single-dose, second-generation cephalosporin - cefotetan or cefoxitin, 1 g intravenously) on postpartum perineal wound complications in third- or fourth-degree perineal tears compared with placebo. Perineal wound complications (wound disruption and purulent discharge) at the two-week postpartum check up were 8.20% and 24.10% in the treatment and the control groups respectively (risk ratio (RR) 0.34, 95% confidence interval (CI) 0.12 to 0.96). However, the high failed-appointment rate may limit the generalisability of the results. The overall risk of bias was low except for incomplete outcome data. The quality of the evidence using GRADE was moderate for infection rate at two weeks' postpartum, and low for infection rate at six weeks' postpartum.

Authors' conclusions

Although the data suggest that prophylactic antibiotics help to prevent perineal wound complications following third- or fourth-degree perineal tear, loss to follow-up was very high. The results should be interpreted with caution as they are based on one small trial.

PLAIN LANGUAGE SUMMARY

Antibiotic prophylaxis for third- and fourth-degree perineal tear during vaginal birth

Background

Most women are able to give birth without serious damage to their perineum. However, severe perineal trauma, which affects the muscle or tissue in the back passage, occurs in 1% to 8% of women giving birth and is common when forceps are used. There is an increased chance of infection when this happens. Pain in this area can impact not only on a woman's daily activity but also on her relationship with her baby and her partner.

When a woman has a severe perineal tear during vaginal birth, there is thought to be an increased risk of infection. Antibiotics are often prescribed to prevent infection.

Review question

To assess how effective antibiotic prophylaxis is to prevent perineal wound infection compared with placebo or no treatment to prevent perineal wound infection and to compare different antibiotic regimens.

Main findings

The review identified one trial, involving 147 women. This trial was conducted to explore the benefit of routine prophylactic antibiotics (intervention group) versus placebo (control group) for women with severe perineal tears. The result showed fewer perineal wound complications in the intervention group at two weeks postpartum. There was no statistically significant difference in perineal wound complications before discharge and at six weeks' postpartum.

The one included study was terminated before it reached the pre-planned sample size and had a high rate of loss to follow-up

Quality of the evidence

The included study was of high methodological quality except for incomplete follow-up. We assessed reduction of perineal wound infection in third- or fourth-degree tear by antibiotic prophylaxis as low to moderate quality of the evidence. However, the results are based on one small trial and there was a high loss to follow-up. More research is needed.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Antibiotic prophylaxis versus no treatment for perineal tear for third- and fourth-degree perineal tear during vaginal birth						
Patient or population: Women with third- and fourth-degree perineal tear during vaginal birth Settings: A hospital in USA Intervention: Antibiotic prophylaxis versus no treatment for perineal tear						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Antibiotic prophylaxis versus no treatment for perineal tear				
Infection rate at 2 weeks postpartum - perineal wound infection in third- or fourth-degree tear	Study population		RR 0.34 (0.12 to 0.96)	107 (1 study)	⊕⊕⊕○ moderate ^{1,2}	
	241 per 1000	82 per 1000 (29 to 232)				
	Moderate					
	241 per 1000	82 per 1000 (29 to 231)				
Infection rate at 6 weeks postpartum - perineal wound infection in third- or fourth-degree tear	Study population		RR 0.38 (0.13 to 1.09)	128 (1 study)	⊕⊕○○ low ^{1,2,3}	
	192 per 1000	73 per 1000 (25 to 209)				
	Moderate					
	192 per 1000	73 per 1000 (25 to 209)				

Fever or puerperal febrile morbidity	Not estimable	0 study	See comment	This outcome was not reported in the one included study.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Small sample size and not met optimal information size (OIS) criteria.

² We could not judge inconsistency due to the inclusion of only one study.

³ Confidence interval overlaps no effect.

BACKGROUND

Description of the condition

Episiotomy is the incision in the perineal area to enlarge the vaginal orifice for easier vaginal birth. It consists of two types: midline or median and mediolateral style. Many studies have shown that routine episiotomy can cause such problems as persistent perineal pain, unsatisfied postpartum sexual function, and increasing anal sphincter injury leading to faecal or flatus incontinence (Christianson 2003; Jones 2000; Labrecque 1997; Nager 2001; Signorello 2001). Pain in this area can impact not only on a woman's daily activity but also on her relationship with her baby and her partner. A restrictive episiotomy policy (strict criteria to perform episiotomy only in proper cases such as short stature mother with short perineum, large size baby, or imminent severe laceration of perineum) has been in place for many years and is strongly supported by a Cochrane systematic review (Carroll 1999). In addition, prenatal perineal massage has also been introduced into practice to prevent perineal tears (Davidson 2000; Eason 2000; Johanson 2000; Labrecque 1999). One randomised controlled trial failed to show the effectiveness of perineal massage but concluded that it did no harm (Stamp 2001). A Cochrane review concluded that antenatal digital perineal massage reduces the incidence of perineal trauma (mainly episiotomies) (Beckmann 2013).

Most women are able to give birth without serious damage to the perineum, but 1% to 8% of women suffer severe perineal tears (anal sphincter injury, with or without rectal mucosa injury) during vaginal birth (De Leeuw 2001; Riskin-Mashiah 2002; Samuelsson 2000; Samuelsson 2002; Sultan 1994). These tears are more common after operative vaginal birth, especially when forceps are used. The incidence of severe perineal lacerations after the use of forceps has been reported as 21% for third-degree and 7% for fourth-degree tears (Bofill 1996). Other risk factors include race (Asian women have the highest risk, perhaps due to small size mother and short perineum), midline episiotomy (short distance to anal sphincter), nulliparity (lesser elasticity than a multiparous mother), and high birthweight baby (De Leeuw 2001; Goldberg 2003; Homs 1994; Jones 2000; Labrecque 1997; Nager 2001; Sultan 1994).

Description of the intervention

When a woman has a severe perineal tear during vaginal birth, there is thought to be an increased risk of infection. Laceration of the vagina and perineum during vaginal birth are classified as first-, second-, third- and fourth-degree tears. First-degree tears involve the vaginal mucosa and connective tissue. Second-degree tears involve the vaginal mucosa, connective tissue and underlying muscles. Third-degree tears involve a complete transection of

anal sphincter and fourth-degree tears involve the rectal mucosa (Cunningham 2001; WHO 2003). When the rectal mucosa is ruptured, the wound is classified as contaminated (Waddell 1994) or clean-contaminated (Mangram 1999). Antibiotic prophylaxis is generally used where wounds have become, or are likely to become, contaminated, such as in colorectal surgery (Oates 1986; Song 1998). A Cochrane review has also shown antibiotic prophylaxis to be effective in reducing puerperal morbidity after cesarean section (Smaill 2002). On the other hand, a Cochrane review on antibiotic prophylaxis after operative vaginal birth could not conclude its effectiveness (Liabsuetrakul 2004).

How the intervention might work

A woman contracting infection after a severe perineal tear may also be at risk of other morbidities as a result of the tear, such as haematoma, dyspareunia (painful sexual intercourse), incontinence and recto-vaginal fistula (Crawford 1993; Homs 1994; Labrecque 1997; Nager 2001; Signorello 2001; Sorensen 1988; Sultan 2002; WHO 2003). While some authorities recommend that prophylactic antibiotics be used for severe perineal tears (WHO 2003), others have recommended against this course of action (Whitfield 1995). As widespread use of antibiotics may contribute to antibiotic-resistant bacteria (Towers 1998; Weinstein 1996), the over-use of antibiotics is being discouraged by many groups.

Why it is important to do this review

Antibiotic prophylaxis is a low-cost, accessible intervention that may prevent considerable maternal morbidity. It is therefore important to establish the benefits of prophylactic antibiotics for infection after severe perineal tears, and also to assess whether there are any adverse effects on mother or infant, by systematically reviewing the evidence.

OBJECTIVES

To assess the effectiveness of antibiotic prophylaxis for reducing maternal morbidity and side effects in third- and fourth-degree perineal tears during vaginal birth.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials and cluster-randomised controlled trials. We did not plan to include quasi-randomised controlled, cross-over trials or include studies that were presented only as abstracts.

Types of participants

Mothers with third- and fourth-degree perineal tears as a result of vaginal birth.

Types of interventions

Antibiotic regimens used to prevent perineal wound infection compared either with placebo, or no treatment; antibiotic treatment in women who get infection only; and comparisons between different antibiotic regimens.

Types of outcome measures

Primary outcomes

1. Fever or puerperal febrile morbidity (body temperature of 38°C or higher occurring on any two occasions in the first 10 days postpartum, exclusion of the first 24 hours).
2. Perineal wound complications, including infection (oedematous, erythematous, wound edge with pain, serosanguinous or frankly purulent material), or wound dehiscence (wound separation).

Secondary outcomes

1. Serious infectious complications (such as bacteraemia, septic shock, septic thrombophlebitis, necrotising fasciitis, or death attributed to infection).
2. Pain (wound pain score or variously measured by authors).
3. Woman's comfort (unable to sit down or breast feed) while in hospital and six weeks postpartum.
4. Length of hospital stay for mother.
5. Adverse reaction (such as allergic reaction, anaphylaxis, diarrhoea).
6. Maternal-infant interactions including breastfeeding.
7. Sexual function including dyspareunia (pain on sexual intercourse), sexual satisfaction, sexual sensation, time to resuming sexual intercourse.
8. Woman's satisfaction.
9. Recto-vaginal fistula (hole between the vagina and rectum).

Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (31 August 2014).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of Embase;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

[For details of additional searching carried out by authors for the initial version of the review ([Buppasiri 2005](#)), see: [Appendix 1](#).]

Searching other resources

We checked the references of retrieved articles to locate other relevant trials.

We did not apply any language restrictions.

Data collection and analysis

For methods used in the previous update, please see [Buppasiri 2010](#). For this update no new studies were identified from the updated search. However, full risk of bias was performed for the included study and the quality of the evidence was assessed using the GRADE approach.

In future updates, the full methods outlined in [Appendix 2](#) will be used.

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for the study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). There were no disagreements. We would have resolved any disagreements through discussion or, if required, we would have involved a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We described for the one included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for the included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for the included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for the included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for the included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomisation participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we planned to re-include missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for the included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for the included study any important concerns we had about other possible sources of bias.

(7) Overall risk of bias

We made explicit judgements about whether the included study was at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we planned to assess the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. In future updates, we will explore the impact of the level of bias through undertaking sensitivity analyses - see [Sensitivity analysis](#). For this update (2014), the quality of the evidence was assessed using the GRADE approach (Schunemann 2009) in order to assess the quality of the body of evidence relating to the following key outcomes for the main comparison.

1. Fever or puerperal febrile morbidity.
2. Perineal wound infection or perineal wound disruption.

The GRADEprofiler ([GRADE 2008](#)) was used to import data from Review Manager 5.3 ([RevMan 2014](#)) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes were produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

RESULTS

Description of studies

Results of the search

The updated search in December 2009 identified two reports of one study ([Duggal 2008](#)) - see [Characteristics of included studies](#) for details. An updated search in June 2014 did not identify any new trials.

Risk of bias in included studies

The one included study was terminated before it reached the pre-planned sample size and had a high rate of loss to follow-up ([Figure 1](#)).

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)
Duggal 2008	+	+	-	+	+	+	+

Allocation

Procedures for adequate allocation concealment were well described in the study. We judged this study to be at low risk of bias for selection bias.

Blinding

The process of blinding was described. The women, investigator and assessor were all blinded. We judged this study to be at low risk of bias for performance and detection bias.

Incomplete outcome data

The planned number of women to be recruited was 310 (155 per arm). The actual number of women recruited was 147 (44.5%, 64 in treatment arm and 83 in control group). The study was terminated before the planned number of women was achieved. The loss to follow-up rate was high (27%, 40 in 147). The study was therefore considered to be at moderate risk of attrition bias for attrition bias.

Selective reporting

The study was considered to be at low risk of selective reporting because the planned outcome measurement was prospectively registered in clinical trial registration.

Other potential sources of bias

We considered that it was unlikely that there would be other sources of potential bias so this domain was judged to be at low risk of bias.

Effects of interventions

See: [Summary of findings for the main comparison Antibiotic prophylaxis versus no treatment for perineal tear for third- and fourth-degree perineal tear during vaginal birth](#)

Single-dose, second-generation cephalosporin intravenously (cefotetan or cefoxitin, 1 g, intravenously, or clindamycin, 900 mg intravenously if allergic to penicillin, in 100 mL of saline) was used as the intervention to prevent perineal wound infection or disruption in the third- or fourth-degree perineal tear compared with placebo (100 mL of normal saline intravenously).

The primary outcome of the included study was gross disruption or purulent discharge at the site of perineal repair by two weeks postpartum.

Perineal wound complications at two weeks postpartum in the treatment and control groups were four of 49 (8.2%) and 14 of 58 (24.1%) respectively ($P = 0.037$, risk ratio (RR) 0.34, 95% confidence interval (CI) 0.12 to 0.96) ([Analysis 1.1](#)).

Perineal wound infection before discharge and at six weeks postpartum was also reported. There were no perineal wound complications before hospital discharge in both groups. One hundred and twenty-eight women were checked at six weeks postpartum (19 of 147 (12.9%) did not come for follow-up at six weeks). There were perineal wound complications in four out of 55 (7.3%) and 14 out of 73 (19.2%) women in the treatment and control groups respectively, ($P = 0.07$, RR 0.38, 95% CI 0.13 to 1.09) ([Analysis 1.2](#)).

DISCUSSION

Summary of main results

There were marginally significantly fewer perineal wound complications at two weeks' postpartum in the intervention group. There was no statistically significant difference in perineal wound complications before discharge and at six weeks' postpartum. However, loss to follow-up was 27.2% and 12.9 % at two and six weeks postpartum respectively.

Overall completeness and applicability of evidence

The one included study, conducted in a developed country, with a relatively high loss of follow-up, provides insufficient data to address the objectives of this review.

Quality of the evidence

The included study was of high methodological quality; most of the domains were judged to be at low risk of bias except for incomplete outcome data, which we assessed as at high risk of bias. We assessed perineal wound infection in third- or fourth-degree tear reduced significantly by antibiotic prophylaxis at two weeks' postpartum as moderate quality of the evidence and six weeks' postpartum as low quality of the evidence due to the small sample size and because the confidence interval overlaps 'no effect' ([Summary of findings for the main comparison](#)). We could not assess "1. Fever or puerperal febrile morbidity" because the outcome was not reported in the one included study. The inadequate sample size and high loss to follow-up rate do not allow us to draw a firm conclusion about the benefit of antibiotic prophylaxis in third- or fourth-degree perineal tear after vaginal birth.

Potential biases in the review process

We adhered to the Cochrane Pregnancy and Childbirth Group search strategies and review process. We are not aware of any potential bias in the review process.

Agreements and disagreements with other studies or reviews

There are no other studies or reviews addressing this clinical question.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence from the one included study is not strong enough to recommend prophylactic antibiotics for third- or fourth-degree perineal tear after delivery.

Implications for research

Well-designed, multicentre, randomised controlled trials are needed before prophylactic antibiotics for third- and fourth-degree perineal tear after vaginal birth can be recommended.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Duggal 2008

Methods	Type of study: prospective, randomised, placebo-controlled trial Method: randomisation was done by using a random-numbers table. Women were randomly assigned to a single dose of antibiotic (cefotetan or cefoxitin, 1 g, intravenously, or clindamycin, 900 mg intravenously if allergic to penicillin, in 100 mL of saline) or placebo (100 mL of normal saline intravenously). The nurse was instructed to open the envelope and administer the medication or placebo. The log book was kept in a secure location in medication room Placebo: yes, normal saline was used. Sample size: to demonstrate a 75% reduction in perineal infection rate with an alpha of 0.05 and a power of 80%, 310 women (155 on each arm) were needed. Only 147 women (83 in placebo group, 64 in treatment group) were enrolled in a 3-year period Intention-to-treat basis: yes. Loss to follow-up: 27.2% (40 of 147) women lost at 2-week postpartum check up. 107 women visited at 2-week postpartum check up. 23.4% (15 of 64) were missed in treatment group, and 30.1% (25 of 83) in control group. 19 of 147 (12.9%) women were lost to follow-up at the 6-week postpartum check up
Participants	Location: Santa Clara Valley Medical Center and Stanford University Medical Center's Lucile Parkard Children's Hospital. California, San Francisco, USA Time frame: September 2003-June 2006. Eligible criteria: women who sustained third- or fourth-degree perineal laceration after vaginal deliveries Exclusion: age < 18 years, group B streptococcus positive, human immunodeficiency virus positive, had chorioamnionitis or history of inflammation bowel disease, or were already on antibiotics for any reason Total recruited: 147 women. Treatment group: 64 women, control group = 83 women.
Interventions	Treatment group: 64 women. Control group: 83 women.
Outcomes	Perineal wound infection rate (gross disruption or purulent discharge at site of perineal repair) by 2 weeks postpartum
Notes	There were 310 preplanned women (155 in each arm). The authors decided to terminate the study after 3 years of enrolment because they could not achieve the preplanned number of women within a reasonable time period. Many women refused to participate and many missed enrolment due to busy labour and delivery wards. Only 147 women were recruited: 64 cases in intervention group and 83 in the control group

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Randomisation was done using a random-numbers table.
Allocation concealment (selection bias)	Low risk	The nurse from another ward was instructed to open the randomisation envelope and administer the medication or placebo. The logbook was kept in a secure location in the medication room
Incomplete outcome data (attrition bias) All outcomes	High risk	107 of 147 women visited for the 2-week postpartum check up, then 27.2 % were lost to follow-up; 15 of 64 (23.4%) in the intervention group and 25 of 83 (30.1%) in the control group
Selective reporting (reporting bias)	Low risk	The authors reported perineal wound complication rates before discharge, and at the 2- and 6-week postpartum check ups
Other bias	Low risk	It is unlikely to have other bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The women were randomised to receive a single dose of an antibiotic in 100 mL saline or placebo 100 mL saline by using random-number tables allocated by a nurse. The clinicians evaluating the women postpartum did not have access to the treatment option
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The clinicians evaluating the women postpartum did not have access to the treatment option

DATA AND ANALYSES

Comparison 1. Antibiotic prophylaxis versus no treatment for perineal tear

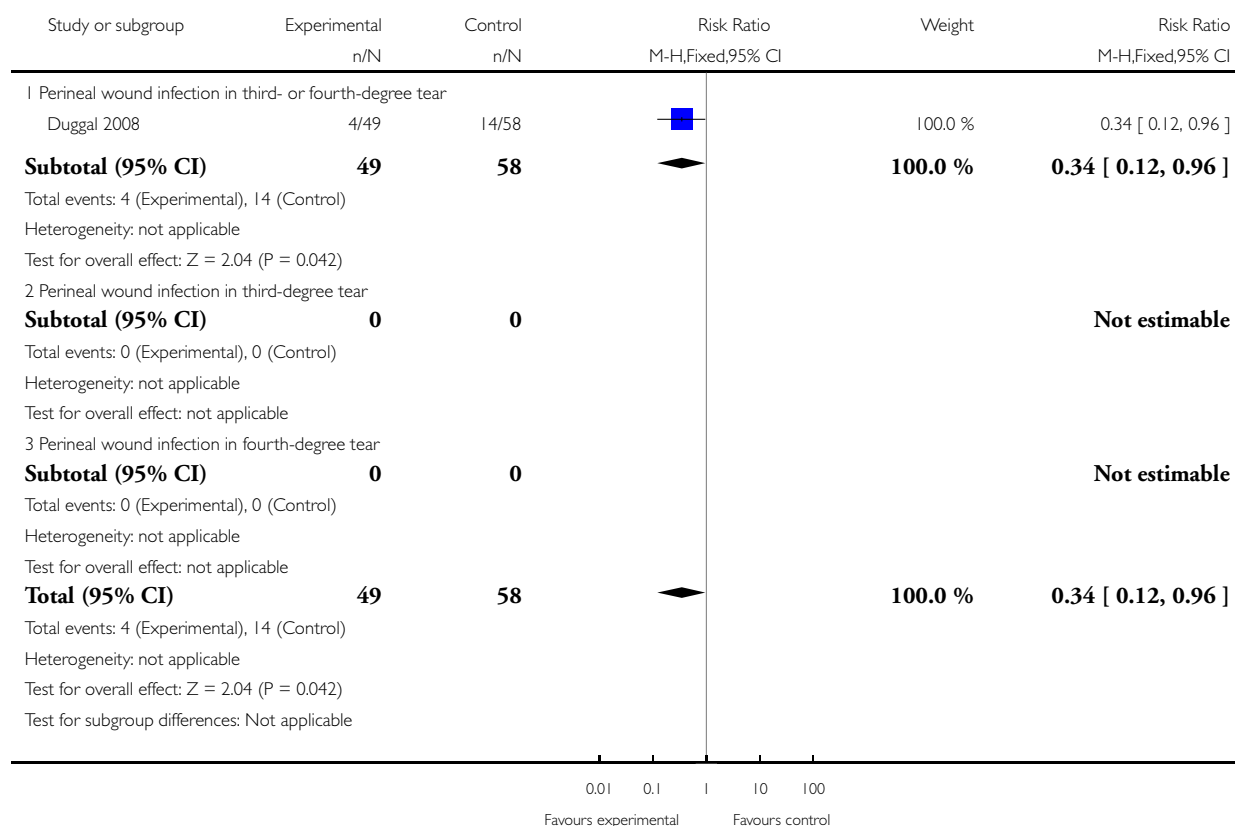
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Infection rate at 2 weeks postpartum	1	107	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.12, 0.96]
1.1 Perineal wound infection in third- or fourth-degree tear	1	107	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.12, 0.96]
1.2 Perineal wound infection in third-degree tear	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Perineal wound infection in fourth-degree tear	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Infection rate at 6 weeks postpartum	1	128	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.13, 1.09]
2.1 Perineal wound infection in third- or fourth-degree tear	1	128	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.13, 1.09]
2.2 Perineal wound infection in third-degree tear	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Perineal wound infection in fourth-degree tear	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Antibiotic prophylaxis versus no treatment for perineal tear, Outcome 1 Infection rate at 2 weeks postpartum.

Review: Antibiotic prophylaxis for third- and fourth-degree perineal tear during vaginal birth

Comparison: 1 Antibiotic prophylaxis versus no treatment for perineal tear

Outcome: 1 Infection rate at 2 weeks postpartum

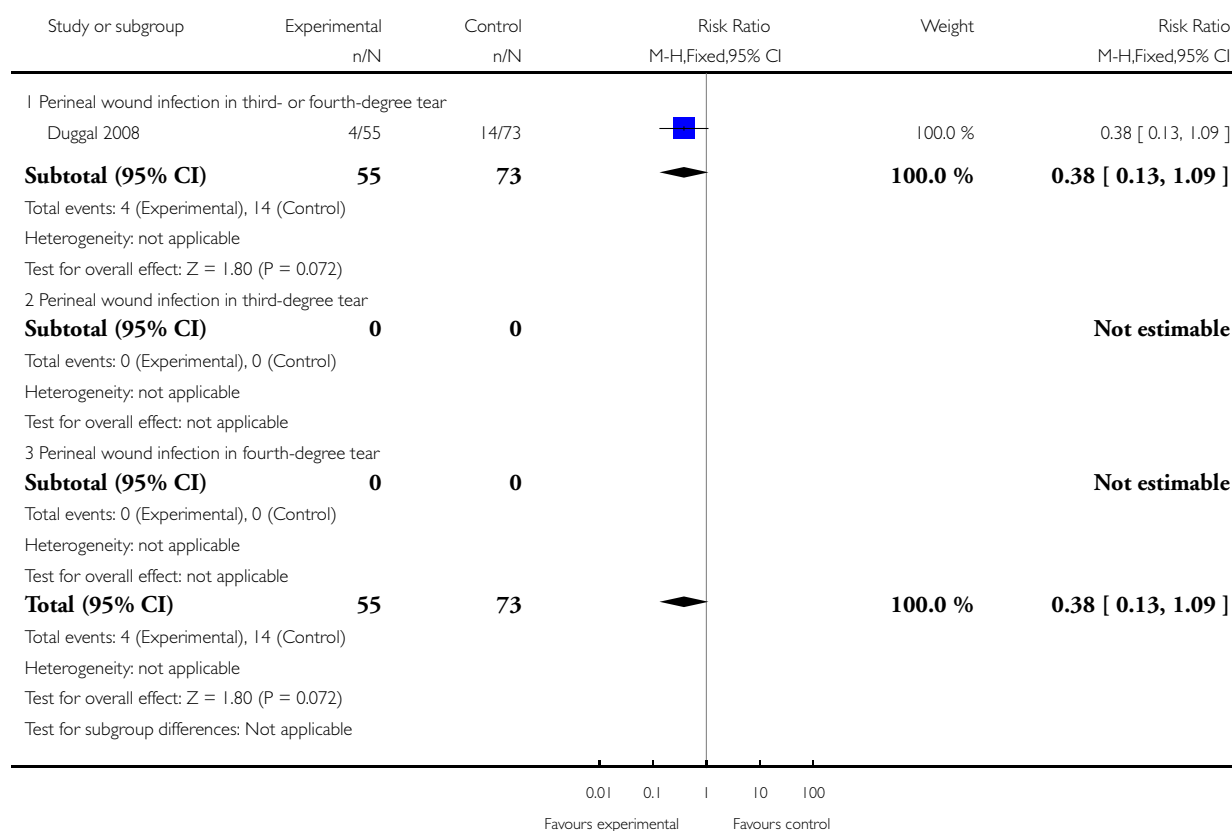


Analysis 1.2. Comparison 1 Antibiotic prophylaxis versus no treatment for perineal tear, Outcome 2 Infection rate at 6 weeks postpartum.

Review: Antibiotic prophylaxis for third- and fourth-degree perineal tear during vaginal birth

Comparison: 1 Antibiotic prophylaxis versus no treatment for perineal tear

Outcome: 2 Infection rate at 6 weeks postpartum



APPENDICES

Appendix 1. Search strategy

For the initial version of the review, authors searched CENTRAL (*The Cochrane Library* 2005, Issue 2), MEDLINE (1966 to 15 July 2005) using the strategy below:

#1 PERINEUM single term (MeSH)

#2 perine*

#3 (tear* or injur* or lacerat* or trauma or damage*)

#4 (#2 and #3)

#5 (anal near sphincter) or (rectal mucosa) or rectum or (anal epithelium) or anus or (recto-vaginal fistulae) or (anorectal mucosa) or (anal skin)

#6 (tear* or injur* or damage* or lacerat* or rupture* or trauma)

#7 (#5 and #6)

#8 (obstetric* near tear*) or (obstetric near lacerat*)

#9 EPISIOTOMY single term (MeSH)

#10 episiotom* or postepisiotom*

#11 EXTRACTION OBSTETRICAL explode tree 1 (MeSH)

#12 vacuum or ventouse or forcep*

#13 deliver*

#14 (birth or childbirth or child-birth or (child next birth))

#15 antibio*

#16 ANTIBIOTICS explode all trees (MeSH)

#17 (#1 or #4 or #7 or #8)

#18 (#9 or #10 or #11 or #12 or #13 or #14)

#19 (#15 or #16)

#20 (#17 and #18 and #19)

Appendix 2. Methods to be used in future updates

Data collection and analysis

Selection of studies

Two review authors will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult a third person.

We will create a study flow diagram to map out the number of records identified, included and excluded.

Data extraction and management

We will design a form to extract data. For eligible studies, at least two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult a third person. We will enter data into Review Manager software ([RevMan 2014](#)) and check for accuracy.

When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We will resolve any disagreement by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We will assess the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We will assess the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.

We will assess methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We will assess the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);

- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We will describe for each included study any important concerns we have about other possible sources of bias.

We will assess whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually randomised-trials. We will adjust their sample sizes using the methods described in the *Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Cross-over trials

Cross-over trials are not eligible for inclusion.

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the τ^2 , I^2 and χ^2 statistics. We will regard heterogeneity as substantial if the I^2 is greater than 30% and either the τ^2 is greater than zero, or there is a low P value (less than 0.10) in the χ^2 test for heterogeneity.

Assessment of reporting biases

If there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We will carry out statistical analysis using the Review Manager software ([RevMan 2014](#)). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average of the range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

If we use random-effects analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of τ^2 and I^2 .

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we plan to investigate it using subgroup analyses and sensitivity analyses. We plan to consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

We plan to carry out the following subgroup analyses.

1. Immunocompromised versus not immunocompromised pregnant women, such as HIV infection, chronic steroid use.
2. Women with prolonged prelabour rupture membranes versus women without prolonged prelabour rupture membranes.
3. Women with preterm prelabour rupture membranes (PPROM) versus women without PPRM.
4. Third-degree tears compared with fourth-degree tears.

We will restrict subgroup analysis to the following outcomes.

1. Fever or puerperal febrile morbidity.
2. Perineal wound infection.

Sensitivity analysis

We will perform sensitivity analyses for aspects of the review that might affect primary outcomes (fever or puerperal febrile morbidity and perineal wound infection), such as where there was risk of bias associated with the quality of some of the included trials. We plan to carry out sensitivity analysis to explore the effects of fixed-effect or random-effects analyses for primary outcomes with statistical heterogeneity.

WHAT'S NEW

Last assessed as up-to-date: 31 August 2014.

Date	Event	Description
31 August 2014	New search has been performed	Review updated.
31 August 2014	New citation required but conclusions have not changed	Search and methods updated. No new trials identified. 'Summary of findings' table incorporated

HISTORY

Protocol first published: Issue 1, 2005

Review first published: Issue 4, 2005

Date	Event	Description
31 August 2010	New search has been performed	Search updated, no new studies identified. One trial identified in the previous updated search has now been included (Duggal 2008). The methods have been updated to reflect the latest Cochrane Handbook. A note about the next update of this review has been added to Published notes .
31 August 2010	New citation required and conclusions have changed	The scope of the review has changed to include both 3rd and 4th degree perineal tears
1 December 2009	Amended	Search updated. Two new reports identified.
13 February 2009	Amended	Contact details updated.
1 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Pranom Buppasiri (PB) updated the review. Pisake Lumbiganon (PL), Jadsada Thinkhamrop (JT) and Bandit Thinkhamrop (BT) approved the updated version for publication.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Faculty of Medicine, Khon Kaen University, Thailand.
- Faculty of Public Health, Khon Kaen University, Thailand.

External sources

- Thai Cochrane Network, Thailand.
- Thailand Research Fund (Distinguished Professor Award), Thailand.
- UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research (RHR), World Health Organization, Switzerland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have broadened the inclusion criteria to include women with third-degree tears and divided the outcomes into primary and secondary.

Methods updated to the current standard methods of the Cochrane Pregnancy and Childbirth Group.

NOTES

The review authors had contacted the trialists of the one included trial ([Duggal 2008](#)) in order to obtain the data separated by degree of perineal tear (3rd or 4th degree) but we have not had a reply from the authors of the trial.

INDEX TERMS

Medical Subject Headings (MeSH)

*Antibiotic Prophylaxis; Anal Canal [*injuries]; Anti-Bacterial Agents [therapeutic use]; Cefotetan [therapeutic use]; Cefoxitin [therapeutic use]; Cephalosporins [therapeutic use]; Delivery, Obstetric [*adverse effects]; Intestinal Mucosa [injuries]; Perineum [injuries]; Randomized Controlled Trials as Topic; Rectum [*injuries]; Rupture [etiology]; Wound Infection [*prevention & control]

MeSH check words

Female; Humans; Pregnancy



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Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery (Review)

Sangkomkamhang US, Lumbiganon P, Prasertcharoensuk W, Laopaiboon M

Sangkomkamhang US, Lumbiganon P, Prasertcharoensuk W, Laopaiboon M.

Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery.

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	3
BACKGROUND	5
OBJECTIVES	6
METHODS	6
RESULTS	9
Figure 1.	11
DISCUSSION	12
AUTHORS' CONCLUSIONS	13
ACKNOWLEDGEMENTS	13
REFERENCES	13
CHARACTERISTICS OF STUDIES	17
DATA AND ANALYSES	21
Analysis 1.1. Comparison 1 Lower genital tract infection screening versus no screening, Outcome 1 Preterm birth less than 37 weeks.	21
Analysis 1.2. Comparison 1 Lower genital tract infection screening versus no screening, Outcome 2 Preterm very low birthweight (below or equal 1500 g).	22
Analysis 1.3. Comparison 1 Lower genital tract infection screening versus no screening, Outcome 3 Preterm low birthweight (below or equal 2500 g).	22
APPENDICES	22
FEEDBACK	23
WHAT'S NEW	23
HISTORY	24
CONTRIBUTIONS OF AUTHORS	24
DECLARATIONS OF INTEREST	24
SOURCES OF SUPPORT	25
INDEX TERMS	25

Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery

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ABSTRACT

Background

Genital tract infection is associated with preterm birth (before 37 weeks' gestation). Screening for infections during pregnancy may therefore reduce the numbers of babies being born prematurely. However, screening for infections may have some adverse effects, such as increased antibiotic drug resistance and increased cost of treatment.

Objectives

To assess the effectiveness of antenatal lower genital tract infection screening and treatment programs for reducing preterm birth and subsequent morbidity.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 November 2014), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2014, Issue 7) and reference lists of retrieved reports.

Selection criteria

We included all published and unpublished randomised controlled trials in any language that evaluated any described methods of antenatal lower genital tract infection screening compared with no screening.

Data collection and analysis

Two review authors independently assessed trials for inclusion and risk of bias, extracted data and checked for accuracy.

Main results

One study (4155 women at less than 20 weeks' gestation) met the inclusion criteria. The intervention group (2058 women) received infection screening and treatment for bacterial vaginosis, trichomonas vaginalis and candidiasis; the control group (2097 women) also received screening, but the results of the screening program were not revealed and women received routine antenatal care. The rate of preterm birth before 37 weeks' gestation was significantly lower in the intervention group (3% versus 5% in the control group) with a

risk ratio (RR) of 0.55 (95% confidence interval (CI) 0.41 to 0.75; the evidence for this outcome was graded as of moderate quality). The incidence of preterm birth for infants with a weight equal to or below 2500 g (low birthweight) and infants with a weight equal to or below 1500 g (very low birthweight) were significantly lower in the intervention group than in the control group (RR 0.48, 95% CI 0.34 to 0.66 and RR 0.34; 95% CI 0.15 to 0.75, respectively; both graded as moderate quality evidence). Based on a subset of costs for preterm births of < 1900 g, the authors reported that for each of those preterm births averted, EUR 60,262 would be saved.

Authors' conclusions

There is evidence from one trial that infection screening and treatment programs for pregnant women before 20 weeks' gestation reduce preterm birth and preterm low birthweight. Infection screening and treatment programs are associated with cost savings when used for the prevention of preterm birth. Future trials should evaluate the effects of different types of infection screening programs.

PLAIN LANGUAGE SUMMARY

Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery

A genital tract infection during pregnancy can cross into the amniotic fluid and result in prelabour rupture of the membranes and preterm labour. Preterm birth (before 37 weeks of gestation) is associated with poor infant health, death, admission of the newborn to neonatal intensive care in the first few weeks of life, prolonged hospital stay and long-term neurologic disability including cerebral palsy.

In this review, only one study of moderate quality evidence was included. The study reported on 4155 women randomly assigned either to an intervention group (2058 women received infection screening and treatment for bacterial vaginosis, trichomonas vaginalis and candidiasis) or a control group (2097 women received screening, but the results of the screening program were not revealed). The present systematic review found that a simple infection screening and treatment program during routine antenatal care may reduce preterm births and preterm low (below 2500 g) and very low (below 1500 g) birthweight. The simple infection screening reduced preterm births from 5% of women in the control group to 3% in the intervention group. The number of low birthweight preterm infants and very low birthweight preterm infants were significantly lower in the intervention group than in the control group. Moreover, an infection screening and treatment program during routine antenatal care is likely to save over EUR 60,000 for each preterm birth averted.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [\[Explanation\]](#)

Lower genital tract infection screening versus no screening for preventing preterm delivery						
Patient or population: pregnant women presenting for routine prenatal care Settings: Vienna, Austria Intervention: lower genital tract infection screening versus no screening						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No screening	Lower genital tract infection screening				
Preterm birth less than 37 weeks	Study population		RR 0.55 (0.41 to 0.75)	4155 (1 study)	⊕⊕⊕○ moderate ¹	
	53 per 1000	29 per 1000 (22 to 40)				
Preterm low birthweight (below or equal 2500 g)	Study population		RR 0.48 (0.34 to 0.66)	4155 (1 study)	⊕⊕⊕○ moderate ¹	
	51 per 1000	24 per 1000 (17 to 34)				
Preterm very low birth-weight (below or equal 1500 g)	Study population		RR 0.34 (0.15 to 0.75)	4155 (1 study)	⊕⊕⊕○ moderate ¹	
	11 per 1000	4 per 1000 (2 to 9)				
*The basis for the assumed risk is the median control group risk across studies. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio						

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ One study with design limitations.

BACKGROUND

Description of the condition

Preterm birth, defined as birth occurring prior to 37 weeks' gestation, occurs in 5% to 10% of all pregnancies and is the most common cause of perinatal morbidity and mortality in the world. Preterm birth is implicated in at least two-thirds of early infant deaths (Cunningham 1997) and 60% of perinatal mortality including long-term neurologic disability such as cerebral palsy. It is associated with admission to neonatal intensive care, severe morbidity in the first weeks of life, prolonged hospital stay after birth, and readmission to hospital in the first year of life (Cunningham 2001; Goldenberg 1998; Roberts 2000; Wood 2000). Surviving infants, especially those born before 32 weeks, have a substantially increased risk of chronic lung disease, and major and minor impairments (Doyle 1996; Saigal 2000). Whatever the result, the emotional impact on the family can be enormous.

A wide spectrum of causes and demographic factors have been implicated in preterm birth. These can be categorized into four groups.

1. Medical and obstetric complications: there are associations with placental hemorrhage and hypertensive disorders in about one-third of cases (Meis 1995).
2. Lifestyle factors: there is an association with alcohol abuse, low maternal age, and occupational factors (Henriksen 1995; Holzman 1995; Satin 1994).
3. Amniotic fluid infection caused by a variety of micro-organisms located in the genital tract: approximately one-third of preterm births are associated with chorioamniotic infection (Lettieri 1993).
4. Asymptomatic cervical dilatation (Papiernik 1986).

Many micro-organisms cause both symptomatic and asymptomatic infection and may result in preterm prelabour rupture of membranes, preterm labour, or both. For example, bacterial vaginosis (including *Gardnerella vaginalis*, *Bacteroides* species, *Mobiluncus* species, *Ureaplasma urealyticum*, and *Mycoplasma hominis*) (Hillier 1995; McDonald 1994; McGregor 1990; Meis 1995), *Chlamydia trachomatis* (Gravett 1986), *Trichomonas vaginalis* (Cotch 1997), *Neisseria gonorrhoeae* (Elliott 1990), Group B *Streptococci* (GBS; Regan 1981), *Staphylococcus aureus* (McGregor 1990), syphilis (McFarlin 1995), HIV (Temmerman 1994), enteropharyngeal bacteria and *Peptostreptococcus* species (McDonald 1994) have been associated with an increased risk of preterm birth. *Candida* species, however, have been associated with an unclear risk of preterm birth (Roberts 2011).

A possible mechanism for the link between infection and preterm birth is the bacterial stimulation of the biosynthesis of prostaglandins. This may occur either directly via phospholipase A₂ and C (Bejar 1981) or as a result of bacterial endotoxin introduced into the amniotic fluid which stimulates decidual cells to produce cytokines and prostaglandins that initiate labour (Cox

1989). Indirect links via substances such as interleukin-1, tumour necrosis factor and platelet activating factor, all of which may be found in infected amniotic fluid, have also been identified (Romero 1992; Yoon 2000).

Description of the intervention

By identifying and treating vaginal infections, screening programs may be able to reduce the rate of preterm birth. Different screening methods are used for different types of organisms, however there is scant evidence to inform the optimal screening regimen for detecting these organisms during pregnancy. Therefore, it is unclear whether all women should be routinely screened, how often the screening should occur, and which tests should be used.

How the intervention might work

Chlamydia trachomatis has been identified by multiple tests from different specimen sources. The samples may be analysed by three types of DNA-based test: ligase chain reaction, polymerase chain reaction (PCR) and enzyme immuno-assay (Watson 2002). DNA amplification techniques allow for highly sensitive and specific tests (Black 1997) that are more sensitive than cell culture (Jespersen 2005). These screening tests can detect *Chlamydia* in genital secretions, urine specimens, and endocervical, vaginal or urethral samples (Domeika 1999; Shrier 2004).

Trichomoniasis may be asymptomatic in up to 50% of infected women (Wolner-Hanssen 1989). The diagnosis is usually made on clinical findings and laboratory procedures (Petrin 1998). Most frequently, the saline wet-mount preparation is used for observation of motile organisms under the light microscope. Wet-mount smear is a cheap and quick method but more sensitive techniques are culture, immunofluorescence and enzyme immunoassay (Lossick 1991; Borchardt 1991). Different staining techniques include Gram stain, Giemsa stain, Papanicolaou smear, acridine orange (Borchardt 1991; Rein 1990); diverse molecularly-based diagnostic methods, such as hybridization assay and PCR, may also be used. These tests vary widely in sensitivities and specificities for screening trichomoniasis (DeMeo 1996; Madico 1998; Mayta 2000; Muresu 1994).

Bacterial vaginosis is a clinical syndrome; the microbiology of bacterial vaginosis is complex and is composed of *Gardnerella vaginalis*, *Mycoplasma hominis* and anaerobic bacteria (Amsel 1983). The diagnosis is usually made on clinical Amsel criteria findings (Amsel 1983) and laboratory tests. Vaginal pH testing may be a valuable screening tool as it is a quick and inexpensive test (Gjerdengen 2000). Vaginal swab Gram stain with quantification of the microbial flora has high sensitivity and specificity and is accepted as an alternative method (Nugent 1991).

Multiple screening tests exist for other organisms including syphilis. Screening tests such as *Treponema pallidum* hemaggluti-

nation assay, *Treponema pallidum* particle agglutination assay, and enzyme-linked immunosorbent assays (ELISAs) are more reliable than Venereal Disease Research Laboratory testing, the fluorescent treponemal antibody absorption test, and immunoblot assays (Muller 2006). The screening test for *Neisseria gonorrhoeae*, usually from a culture, remains accurate when transport conditions are suitable; this tests can be used with cervical, urine and vaginal swabs. Diagnosis of HIV infection can be obtained from enzyme-linked immunosorbent assay (ELISA), Western blot, and RNA PCR testing (Kleinman 1998). The HIV-p24 Ag is effective for early diagnosis of an acute HIV infection (Thies 1994). Strategies for the diagnosis of GBS include obtaining vaginal or both vaginal and anorectal GBS cultures (Quinlan 2000) and a rapid enrichment cum antigen detection test (Das 2003).

Why it is important to do this review

Other Cochrane reviews have addressed a number of issues regarding treatment of infection in pregnancy. Antibiotic treatment of chlamydia, trichomoniasis, bacterial vaginosis and gonorrhoeal infection in pregnancy appear to be effective to clear organisms (Brocklehurst 1998; Brocklehurst 2002; Gülmezoglu 2002; Brocklehurst 2013) but it is not known whether treatment of *trichomonas* will have any effect on pregnancy outcomes (Gülmezoglu 2002). There is also little evidence to show that screening and treatment in all asymptomatic pregnant women for bacterial vaginosis can prevent preterm birth (Brocklehurst 2013), although antibiotic prophylaxis in pregnancies with a previous preterm birth associated with bacterial vaginosis can reduce preterm delivery (Thinkhamrop 2002). There is insufficient evidence regarding the treatment of ureaplasmas to reduce preterm birth (Raynes-Greenow 2004), and there is no evidence that antiretrovirals and the treatment of syphilis influence the incidence of preterm birth (Volmink 2007; Walker 2001). None of the aforementioned reviews are concerned primarily with screening programs for antenatal lower genital tract infection, thus a review of the effects of screening programs for lower genital tract infection to prevent preterm birth is required.

OBJECTIVES

To assess the effects of antenatal lower genital tract infection screening and treatment programs in reducing preterm birth and subsequent morbidity.

METHODS

Criteria for considering studies for this review

Types of studies

We included all published and unpublished randomised controlled trials evaluating any described method of antenatal lower genital tract infection screening in pregnancy.

Types of participants

Women, at 37 or fewer weeks' gestation, who are not in labour, have no vaginal bleeding and are without symptoms of lower genital tract infection.

Types of interventions

Any lower genital tract infection screening and treatment program compared with no screening. The infection screening programs are defined as screening tests (such as wet mount, Gram stain and culture of vaginal secretions) followed by appropriate treatment after a positive screening test, or no treatment after a negative screening test. No screening is defined as routine antenatal care without screening for lower genital tract infections.

Types of outcome measures

Primary outcomes

1. Preterm birth (less than 37 weeks' gestation)

Secondary outcomes

1. Low birthweight (LBW) less than 2500 g
2. Very LBW less than 1500 g (not prespecified)
3. Neonatal morbidity: sepsis, respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, seizures
4. Duration of admission to neonatal intensive care unit or hospital
5. Death: stillbirth, neonatal mortality, infant mortality
6. Side-effects of treatment including drug resistance
7. Persistent infection
8. Recurrent infection
9. Failure of treatment
10. Economic analysis (cost effectiveness, cost utility)
11. False positive/negative result of the screening program
12. Women's satisfaction

Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (30 November 2014).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

In addition, we searched CENTRAL (*The Cochrane Library* 2014, Issue 7) using the search strategy detailed in [Appendix 1](#).

Searching other resources

We did not identify any additional or ongoing trials from personal communication. We searched the reference lists of trials and review articles identified.

We did not apply any language or date restrictions.

Data collection and analysis

For methods used in the previous version of this review, see [Sangkomkamhang 2008](#).

For this update, the following methods were used for assessing the three reports that were identified as a result of the updated search. The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted the third review author.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted the third review author. Data were entered into Review Manager software ([RevMan 2014](#)) and checked for accuracy.

When information regarding any of the above was unclear, we planned to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). Any disagreement was resolved by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as having a(n):

- low risk of bias (any truly random process, for example random number table or computer random number generator);
- high risk of bias (any non-random process, for example odd or even date of birth or hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as having a(n):

- low risk of bias (for example telephone or central randomisation or consecutively numbered sealed opaque envelopes);
- high risk of bias (for example open random allocation, unsealed or non-opaque envelopes, alternation, based on date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the

lack of blinding was unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as having a(n):

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods used to blind outcome assessment as having a(n):

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we planned to re-include missing data in the analyses which we undertook.

We assessed the methods as having a(n):

- low risk of bias (for example no missing outcome data or missing outcome data balanced across groups);
- high risk of bias (for example numbers or reasons for missing data imbalanced across groups or 'as treated' analysis done with substantial departure from the treatment assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as having a(n):

- low risk of bias (where it was clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (all of the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);

- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we had about other possible sources of bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at a high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we planned to assess the likely magnitude and direction of the bias and whether we considered it likely to impact on the findings. In future updates, we will explore the impact of the level of bias through undertaking sensitivity analyses (see [Sensitivity analysis](#)).

For this update the quality of the evidence was assessed using the GRADE approach (Schunemann 2009). We assessed the quality of the body of evidence relating to the following outcomes for the comparison of lower genital tract infection screening versus no screening.

1. Preterm birth (less than 37 weeks).
2. Preterm low birthweight (below or equal to 2500 g).
3. Preterm very low birthweight (below or equal to 1500 g).

Outcomes number two and three are subsets of outcome number one.

GRADEpro (GRADE 2014) was used to import data from Review Manager 5.3 (RevMan 2014) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes was produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

We used the mean difference if outcomes were measured in the same way between trials (and in this case, since there was only one included trial). We would have used the standardised mean

difference to combine trials that measured the same outcome but used different methods.

Unit of analysis issues

Cluster-randomised trials

For future updates, we will include cluster-randomised trials in the analyses along with individually randomised trials. We will adjust their sample sizes or standard errors using the methods described in the *Handbook* [Section 16.3.4 or 16.3.6] using an estimate of the intraclass correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of the intervention and the choice of the randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform sensitivity or subgroup analysis to investigate the effects of the randomisation unit.

Dealing with missing data

For the included study, levels of attrition were noted. In future updates, if more eligible studies are included, the impact of including studies with high levels of missing data in the overall assessment of treatment effect will be explored by using sensitivity analysis. For all outcomes, analyses were carried out, as much as possible, on an intention-to-treat basis. In other words, we attempted to include all participants randomised to each group in the analyses. The denominator for each outcome was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the τ^2 , I^2 and χ^2 statistics. We regarded heterogeneity as substantial if I^2 was greater than 30% and either τ^2 was greater than zero, or there was a low P value (less than 0.10) in the χ^2 test for heterogeneity. If we identified substantial heterogeneity (above 30%), we planned to explore it by pre-specified subgroup analysis.

Assessment of reporting biases

In future updates, if there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014). We used a fixed-effect meta-analysis in this case, since only one study was included. In future updates, we will also use a fixed-effect meta-analysis to combine data where it is reasonable to assume that studies are estimating the same underlying treatment effect, i.e. where trials are examining the same intervention, and the trials' populations and methods are judged to be sufficiently similar.

In future updates, if there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity was detected, we will use a random-effects meta-analysis to produce an overall summary (if an average treatment effect across trials is considered clinically meaningful). The random-effects summary will be treated as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials. If we use random-effects analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of τ^2 and I^2 .

Subgroup analysis and investigation of heterogeneity

For future updates if we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, we will use a random-effects analysis to produce it.

We will carry out the following subgroup analyses.

1. Early versus late trimester at screening (defined by author).
2. Low risk versus high risk of preterm birth, for example multiple pregnancy or previous history of preterm birth.

We plan to restrict subgroup analyses to the primary outcome.

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2014). We will report the results of subgroup analyses quoting the χ^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We planned to carry out sensitivity analyses to explore the effect of trial quality assessed by concealment of allocation, high attrition rates, or both, with poor quality studies being excluded from the analyses in order to assess whether this makes any difference to the overall result.

RESULTS

Description of studies

Also see [Characteristics of included studies](#) table.

Results of the search

A new search identified three reports assessed for possible inclusion in the review. Two reports related to the same trial; this trial was excluded ([Sungkar 2012](#)). The third report was an additional report for the included trial [Kiss 2004](#), with additional outcome data and economic analysis.

Included studies

One included article ([Kiss 2004](#)) reported a randomised controlled trial designed to evaluate a vaginal infection screening strategy for the prevention of preterm delivery in a general population of pregnant women. A total of 4155 pregnant women presenting for a routine prenatal visit without subjective complaints were randomised to either the intervention group (n = 2058) or the control group (n = 2097). All women were screened by Gram stain for asymptomatic vaginal infection. For the intervention group, women found to have vaginal infection received standard treatment. For the control group, vaginal smear test results were not

revealed so the standard antenatal care program could not be influenced.

Additionally, cost effectiveness of a screen-and-treat program for asymptomatic vaginal infections in pregnancy (the direct medical costs of preterm delivery of infants with a birthweight below 1900 g and the costs of the screen-and-treat program) was reported.

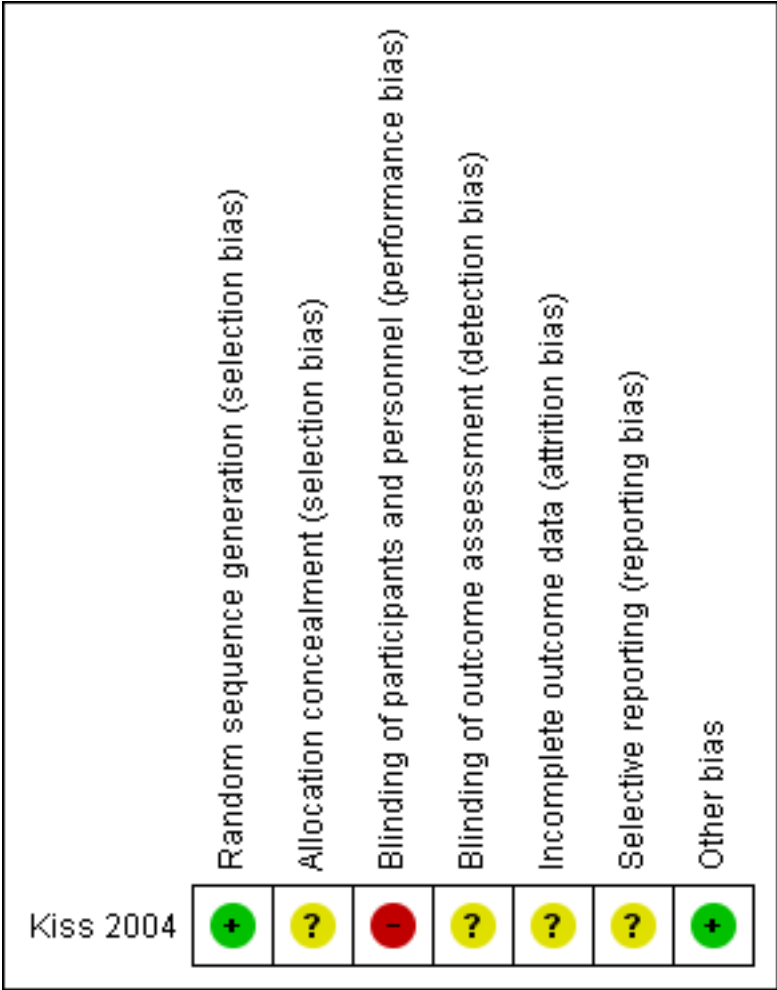
Excluded studies

Three trials ([Gjerdingen 2000](#); [McGregor 1995](#); [Sungkar 2012](#)) were excluded because the participants did not meet the inclusion criteria or the study was not a randomised controlled trial. For further details, please see the [Characteristics of excluded studies](#) table.

Risk of bias in included studies

For [Kiss 2004](#), sequence generation was by computer which was judged to be at low risk of bias. See 'Risk of bias' table in [Characteristics of included studies](#) and [Figure 1](#).

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

There were no details about the random assignment process, therefore the risk of selection bias was unclear.

Blinding

Blinding of the intervention was not possible. In the intervention group, women and their obstetricians were aware of the results of the screening tests, as women were treated for any detected infections. Thus, the risk of detection bias was present; the obstetricians may have provided a different level of care to women in the intervention group in whom an infection had been identified. Blinding of outcome assessors was not described, however this is unlikely to affect the outcome of birthweight.

Incomplete outcome data

Of the 4429 pregnant women who were randomised, 274 were excluded (140 lost to follow up; 68 did not fulfill all the inclusion criteria; 66 had multiple pregnancies). The overall attrition was less than 10%, however, it was not specified how many patients were lost to follow-up in each arm.

Selective reporting

We did not have the protocol for the included study, therefore we assessed the risk of bias for selective reporting as unclear. We have requested that the authors provide us with additional data but have received no reply.

Other potential sources of bias

None identified.

Effects of interventions

See: [Summary of findings for the main comparison](#) Lower genital tract infection screening versus no screening for preventing preterm delivery

Lower genital tract infection screening versus no screening

Primary outcomes

We identified a single randomised controlled trial ([Kiss 2004](#)) comparing antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery with no screening program. A total of 4429 women were randomised with 274 women excluded from the analysis. In the intervention group (2058 women), the results of infection screening and treatment for bacterial vaginosis, *Trichomonas vaginalis* and candidiasis were reported; in the control group (2097 women), the results of the screening tests for the women allocated to receive routine antenatal care were not reported. There was a statistically significant difference in number of preterm births before 37 weeks between the two groups (risk ratio (RR) 0.55, 95% confidence interval (CI) 0.41 to 0.75, [Analysis 1.1](#)).

Secondary outcomes

Numbers of preterm low birthweight infants (weight equal to or below 2500 g) and preterm very low birthweight infants (weight equal to or below 1500 g) were significantly lower in the intervention group than in the control group (RR 0.48, 95% CI 0.34 to 0.66 and RR 0.34, 95% CI 0.15 to 0.75, respectively) ([Kiss 2004](#)). None of the women reported adverse effects during the treatment period. Neonatal morbidity and mortality were not reported.

For a subset of preterm infants with a birthweight less than 1900 g in the [Kiss 2004](#) trial, hospital costs for mother and baby and the costs of the screening program were assessed to be EUR 60,692 (with screening and treatment contributing only 7% of costs). Overall cost savings per prevented preterm birth for this subset therefore amounted to EUR 60,692. In this trial, the screening program halved the number of preterm infants with a birthweight < 1900 g. This threshold was chosen as these babies were all transferred to the neonatal intensive care unit.

DISCUSSION

Summary of main results

In a single trial, an antenatal lower genital tract infection screening and treatment program was shown to significantly reduce preterm birth, low birthweight preterm births (below 2500 g) and very low birthweight preterm births (below 1500 g). This intervention led to savings in direct costs associated with prematurity. The quality of the evidence was rated as moderate.

Overall completeness and applicability of evidence

The included trial was conducted in a developed country (Austria) where characteristics of the population, such as incidence and pattern of lower genital tract infections and socioeconomic status, might differ compared to other countries. Therefore, the results of this review might not be globally generalisable. There was also economic evaluation of this intervention.

Quality of the evidence

Using the Cochrane Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach, the evidence for preterm birth outcomes was graded as moderate. The strength of this review was that the included trial was a large multi-centre prospective, randomised controlled trial. There was a clear sample-size calculation and an adequate number of participants were available for the analysis. However, around 3.2% of all randomised women (140/4429) were lost to follow up, and the study authors did not report whether the loss rate was balance between the two groups. Further, there was no blinding of group assignment or of screening results in the intervention group. The differences between the care received in the treatment and control arms may have introduced bias, depending upon the outcome measure in question.

The cost-benefit analysis showed a substantial savings of more than EUR 60,000 per preterm birth averted for a subset of low birthweight babies routinely admitted to the neonatal intensive care unit. Costs for the 75% of preterm babies with birthweights > 1900 g in this trial were not reported but are assumed to be lower due to lower rates of hospitalisation.

Potential biases in the review process

We followed the methods set out in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). A comprehensive search was performed, all studies were examined, and the data were independently extracted by at least two review authors. We restricted the included studies to RCTs as they provide the strongest level of evidence. Therefore, we have attempted to reduce bias in the review process.

Agreements and disagreements with other studies or reviews

The results agree with another Cochrane systematic review (Brocklehurst 2013), which reported that antibiotic treatment of bacterial vaginosis in pregnant women with abnormal vaginal flora may reduce preterm birth at less than 37 weeks' gestation. Our results differed from Gülmezoglu 2011, which reported that metronidazole for the treatment of asymptomatic pregnant women with trichomoniasis led to an increase in preterm birth at less than 37 weeks' gestation compared with no treatment.

AUTHORS' CONCLUSIONS

Implications for practice

Integrating a simple infection screening and treatment program into routine antenatal care may reduce preterm births in a general population of pregnant women. However, based on the evidence reviewed, we are not able to determine the effects of recurrent or persistent infection on preterm birth. Healthcare providers should discuss the potential benefits and harms of infection screening and tailor care to meet the specific needs of each care setting and healthcare system, or both.

Implications for research

Further randomised controlled trials are needed to determine the effects of antenatal infection screening and treatment programs in

different contexts, for example, different gestational ages, different types of infection screening, and in different populations, especially in developing countries with high rates of preterm birth.

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As part of the pre-publication editorial process of this review, Sangkomkarnhang 2008 was commented on by three peers (an editor and two referees who are external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

We thank Nancy Medley for her support in the creation of the 'Summary of findings' table for this update. Nancy Medley's work was financially supported by the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research (RHR), World Health Organization. The named authors alone are responsible for the views expressed in this publication.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Kiss 2004

Methods	Randomised trial with computer-generated randomisation sequence. All pregnant women presenting for antenatal care were screened, with smear samples sent to the central laboratory where they were randomly assigned to the intervention or control group. Women in the intervention arm with a positive screening result received treatment. Women in the control group were blinded to screening results and received routine antenatal care. Description of withdrawals: yes. Intention-to-treat analysis: not used	
Participants	4429 pregnant women (mean age 28.9, SD 5.6) presenting for routine prenatal visits between 15 and 19 weeks' gestation (mean 17, SD 1.6). Intervention group: n = 2058 ; control group: n = 2097. Inclusion criteria: gestational age 15-19 weeks without subjective complaints (e.g. contractions and vaginal bleeding). Exclusion criteria: clinical symptoms of vaginal infection, multiple pregnancies. Location: Vienna, Austria	
Interventions	Intervention group: vaginal smears (Gram stain and evaluated by the scoring criteria proposed by Nugent 1991) screening for bacterial vaginosis, <i>Trichomonas vaginalis</i> and <i>Candida</i> species and received standard antibiotic treatment if positive screening test, i. e. 2% for 6 days local clindamycin for bacterial vaginosis, 300 mg twice daily for seven days oral clindamycin for recurrent bacterial vaginosis, 0.1 g for 6 days local clotrimazole for candidiasis, and 500 mg for 7 days local metronidazole for trichomoniasis (including treatment of the partner). Control group: were smeared, but the results of testing were not made available to the women's care providers and did not have any effect on the standard clinical antenatal care program routine antenatal examination	
Outcomes	Primary outcome: spontaneous preterm delivery at less than 37 weeks' gestation Secondary outcomes: 1. low birthweight: preterm birth with birthweight below 2500 g; 2. very low birthweight: preterm birth with birthweight below 1500 g; 3. rates of miscarriage between 16-22 and 20-24 weeks; 4. intrauterine death; 5. prevalence of various forms of vaginal infections; 6. duration of sick leave and hospitalisation.	
Notes	4429 randomised, 274 excluded from analysis, 140 lost to follow up, 68 did not fulfill all inclusion criteria, 66 multiple pregnancies. We have contacted the author and are waiting for a reply for our request for additional data (secondary outcomes e.g. neonatal necrotizing enterocolitis, neonatal sepsis, neonatal death, duration of neonatal admission to NICU/hospital). We will incorporate these additional data in an update to the review, should they be forthcoming	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Kiss 2004 (Continued)

Random sequence generation (selection bias)	Low risk	A pre-established computer generated randomisation list was used to allocate patients to the treatment groups
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	All obstetricians and women in the intervention group received their smear results and different treatment regimens
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described, but assessors would not have influenced the objective outcome of birth-weight
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4429 pregnant women: 2058 in the treatment group, 2097 in the control group. There were 274 patients excluded from the study with group allocation not stated (140 lost to follow up, 68 did not fulfill all inclusion criteria, 66 multiple pregnancies) Intention to treat analysis was not described.
Selective reporting (reporting bias)	Unclear risk	No information available because protocol is not accessible; we have contacted authors for additional outcome data
Other bias	Low risk	The study seems to be free of other types of bias.

NICU: neonatal intensive care unit

SD: standard deviation

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Gjerdingen 2000	Participants did not meet inclusion criteria. Study compared standard prenatal care including routine inquiry about vaginal symptoms versus standard care supplemented by vaginal pH testing. Both arms had pregnant women who were diagnosed with lower genital tract infection and all participants received vaginal pH screening. Participants: 121 pregnant women with or without vaginal infection symptoms. Intervention: vaginal pH testing. Outcomes: bacterial vaginosis detection rate, preterm deliveries

(Continued)

Gupta 2013	Participants did not meet inclusion criteria. Study compared screening for and treatment of abnormal vaginal flora versus no treatment. Participants: 242 pregnant women with abnormal vaginal flora. Intervention: screening by vaginal swab for Gram stained and examined for budding yeast cells, pseudohyphae and bacteria of various morphotypes, and scored using the Nugent criteria. Outcomes: preterm birth.
McGregor 1995	Methods not clearly described, but seems likely that this was not a randomised controlled trial. Described as a prospective observational trial. Participants: 1260 women. Intervention: lower genital tract micro-organism screening (vaginal fluid enzyme; nonspecific protease, sialidase, phospholipase C, phospholipase A2). Outcomes: preterm birth, early pregnancy loss.
Sungkar 2012	Participants did not meet inclusion criteria. Study compared self-examination of vaginal acidity, and microbiologic testing for BV (Gram staining) versus usual prenatal care standard care. Participants: 176 singleton pregnant women with or without vaginal infection symptoms. Intervention: education about preterm birth and its risk factors, self-examination of vaginal acidity, and microbiologic testing for BV (Gram staining). Outcomes: preterm birth.

DATA AND ANALYSES

Comparison 1. Lower genital tract infection screening versus no screening

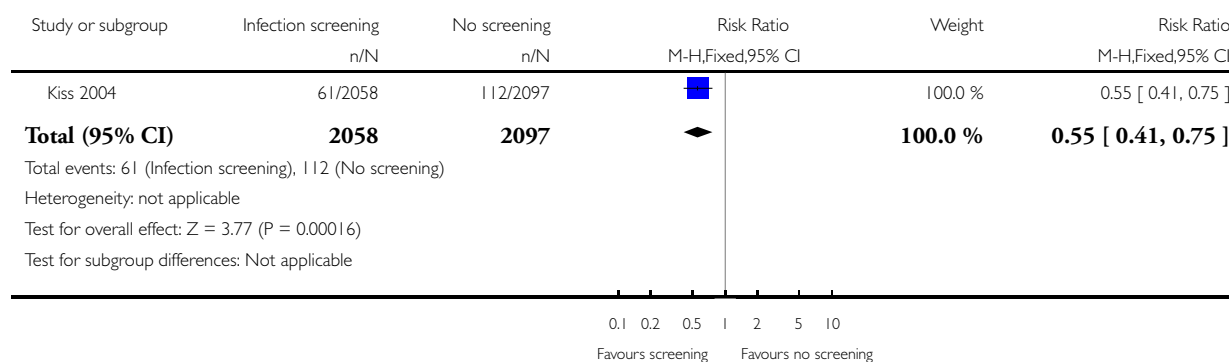
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Preterm birth less than 37 weeks	1	4155	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.41, 0.75]
2 Preterm very low birthweight (below or equal 1500 g)	1	4155	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.15, 0.75]
3 Preterm low birthweight (below or equal 2500 g)	1	4155	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.34, 0.66]
4 Neonatal morbidity	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Duration of admission to neonatal intensive care unit/hospital	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Neonatal death	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Side-effects of treatment (including drug resistance)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Persistent infection	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Recurrent infection	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Women's satisfaction	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Lower genital tract infection screening versus no screening, Outcome 1 Preterm birth less than 37 weeks.

Review: Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery

Comparison: 1 Lower genital tract infection screening versus no screening

Outcome: 1 Preterm birth less than 37 weeks

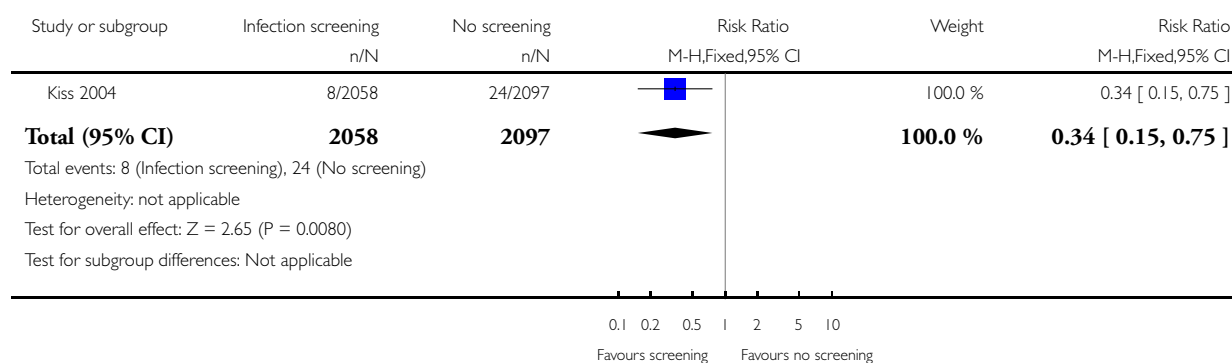


Analysis 1.2. Comparison 1 Lower genital tract infection screening versus no screening, Outcome 2 Preterm very low birthweight (below or equal 1500 g).

Review: Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery

Comparison: 1 Lower genital tract infection screening versus no screening

Outcome: 2 Preterm very low birthweight (below or equal 1500 g)

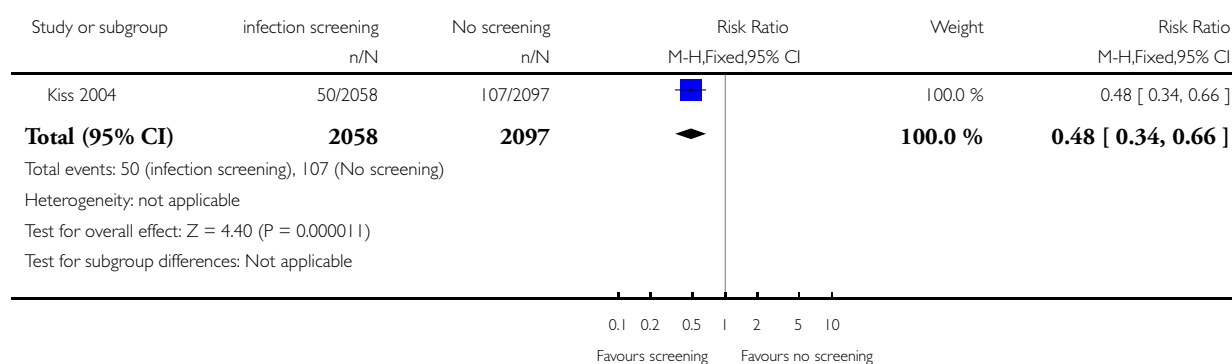


Analysis 1.3. Comparison 1 Lower genital tract infection screening versus no screening, Outcome 3 Preterm low birthweight (below or equal 2500 g).

Review: Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery

Comparison: 1 Lower genital tract infection screening versus no screening

Outcome: 3 Preterm low birthweight (below or equal 2500 g)



APPENDICES

Appendix I. CENTRAL search strategy

#1 MeSH descriptor Pregnancy explode all trees in MeSH products
#2 MeSH descriptor Pregnancy Complications explode all trees in MeSH products
#3 pregnan* in All Fields in all products
#4 (preterm or premature) near (labour or labor) in All Fields in all products
#5 MeSH descriptor Infection explode all trees in MeSH products
#6 MeSH descriptor Mass Screening explode all trees in MeSH products
#7 screen* in All Fields in all products
#8 infect* in All Fields in all products
#9 (#1 OR #2 OR #3 OR #4)
#10 (#5 OR #8)
#11 (#6 OR #7)
#12 (#9 AND #10 AND #11)

FEEDBACK

Nallendran, 16 February 2009

Summary

The Cochrane Review on antibiotic treatment of bacterial vaginosis in pregnancy¹ suggests that there is no improvement in preterm birth rate with treatment, whereas your results suggest an improvement. Could you explain these apparently different conclusions?

References

¹McDonald HM, Brocklehurst P, Gordon A. Antibiotics for treating bacterial vaginosis in pregnancy. *Cochrane Database of Systematic Reviews* 2007, Issue 1. Art. No.: CD000262. DOI: 10.1002/14651858.CD000262.pub3.
(Summary of feedback received from Vijaianitha Nallendran)

Reply

McDonald's review of antibiotic treatment for bacterial vaginosis compares "antibiotic treatment with placebo or no treatment". This is different to our review which compares "any lower genital tract infection screening and treatment programs with no screening". In the McDonald review, the subgroup analysis for the small number of women who received treatment before 20 weeks' gestation shows a promising reduction in the risk of preterm birth less than 37 weeks (odds ratio 0.72, 95% confidence interval (CI) 0.55 to 0.95; five trials, 4155 women). Although this is not strong evidence, it is consistent with the reduction in preterm birth before 37 weeks in our review (risk ratio 0.55, 95% CI 0.41 to 0.75; one trial, 4155 women).

Contributors

Ussanee S Sangkomkamhang on behalf of the review team.

WHAT'S NEW

Last assessed as up-to-date: 31 July 2014.

Date	Event	Description
31 July 2014	New citation required but conclusions have not changed	Review updated. No new trials included.
31 July 2014	New search has been performed	Search updated and three new reports assessed for inclusion. Two reports related to the same trial; this trial was excluded. The third report was an additional report for an included trial Methods updated and 'Summary of findings' table added.

HISTORY

Protocol first published: Issue 4, 2006

Review first published: Issue 2, 2008

Date	Event	Description
6 August 2009	Feedback has been incorporated	Authors replied to feedback from Vijaianitha Nallendran.
28 July 2009	New search has been performed	Search updated. No new reports identified.
26 March 2009	Feedback has been incorporated	Feedback from Vijaianitha Nallendran added.
10 November 2008	Amended	Contact details updated.
15 February 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

US and PL developed the title and question. US, PL and WP developed the protocol; ML commented on drafts of the protocol. US wrote the first draft of the original review; PL, ML, and WP reviewed and gave comments on the drafts of the review. US and ML wrote the draft of the 2014 updated review, WP gave comments on the drafts of the review, PL commented on and supervised the development of the updated review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Khon Kaen Hospital, Khon Kaen, Ministry of Public Health, Thailand.
- Khon Kaen University, Faculty of Medicine, Khon Kaen, Thailand.
- Khon Kaen University, Faculty of Public Health, Thailand.

External sources

- Thai Cochrane Network, Thailand.
- Thailand Research Fund (Senior Research Scholar), Thailand.
- UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research (RHR), World Health Organization, Switzerland.

INDEX TERMS

Medical Subject Headings (MeSH)

Candidiasis, Vulvovaginal [*diagnosis; *therapy]; Premature Birth [etiology; *prevention & control]; Trichomonas Vaginitis [*diagnosis; *therapy]; Vaginosis, Bacterial [*diagnosis; *therapy]

MeSH check words

Female; Humans; Pregnancy



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Diet or exercise, or both, for preventing excessive weight gain in pregnancy (Review)

Muktabhant B, Lawrie TA, Lumbiganon P, Laopaiboon M

Muktabhant B, Lawrie TA, Lumbiganon P, Laopaiboon M.
Diet or exercise, or both, for preventing excessive weight gain in pregnancy.
Cochrane Database of Systematic Reviews 2015, Issue 6. Art. No.: CD007145.
DOI: 10.1002/14651858.CD007145.pub3.

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	4
BACKGROUND	6
OBJECTIVES	7
METHODS	7
RESULTS	11
Figure 1.	14
Figure 2.	15
ADDITIONAL SUMMARY OF FINDINGS	23
DISCUSSION	26
AUTHORS' CONCLUSIONS	28
ACKNOWLEDGEMENTS	28
REFERENCES	29
CHARACTERISTICS OF STUDIES	42
DATA AND ANALYSES	152
Analysis 1.1. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 1 Excessive weight gain.	159
Analysis 1.2. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 2 Weight gain (kg).	161
Analysis 1.3. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 3 Low weight gain.	163
Analysis 1.4. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 4 Preterm birth.	165
Analysis 1.5. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 5 Pre-eclampsia.	167
Analysis 1.6. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 6 Hypertension (not prespecified).	169
Analysis 1.7. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 7 Induction of labour.	171
Analysis 1.8. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 8 Caesarean delivery.	173
Analysis 1.9. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 9 Postpartum weight retention (kg).	175
Analysis 1.10. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 10 Postpartum weight retention (n/N; investigator defined time frame).	177
Analysis 1.11. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 11 Energy intake (kj).	178
Analysis 1.12. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 12 Fibre intake (g).	180
Analysis 1.13. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 13 Physical activity score (26-29 weeks).	181
Analysis 1.14. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 14 Macrosomia Infant birthweight > 4000 g.	182
Analysis 1.15. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 15 Infant birthweight > 90th centile.	185
Analysis 1.16. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 16 Birthweight (g) (not prespecified).	187
Analysis 1.17. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 17 Infant birthweight < 2500 g.	189
Analysis 1.18. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 18 Infant birthweight < 10th centile.	191
Analysis 1.19. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 19 Shoulder dystocia.	192
Analysis 1.20. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 20 Neonatal hypoglycaemia.	193

Analysis 1.21. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 21 Birth trauma.	194
Analysis 1.22. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 22 Neonatal hyperbilirubinaemia.	195
Analysis 1.23. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 23 Neonatal respiratory distress syndrome.	196
Analysis 1.24. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 24 Postpartum hemorrhage.	197
Analysis 2.1. Comparison 2 Diet intervention (low GI diet) vs standard/other care, Outcome 1 Excessive weight gain.	198
Analysis 2.2. Comparison 2 Diet intervention (low GI diet) vs standard/other care, Outcome 2 Weight gain (kg).	199
Analysis 2.3. Comparison 2 Diet intervention (low GI diet) vs standard/other care, Outcome 3 Low weight gain.	199
Analysis 2.4. Comparison 2 Diet intervention (low GI diet) vs standard/other care, Outcome 4 Preterm birth.	200
Analysis 2.5. Comparison 2 Diet intervention (low GI diet) vs standard/other care, Outcome 5 Caesarean delivery.	201
Analysis 2.6. Comparison 2 Diet intervention (low GI diet) vs standard/other care, Outcome 6 Macrosomia (Infant birthweight > 4000 g).	202
Analysis 3.1. Comparison 3 Diet and exercise counselling vs standard/other care, Outcome 1 Excessive weight gain.	203
Analysis 3.2. Comparison 3 Diet and exercise counselling vs standard/other care, Outcome 2 Weight gain (kg).	204
Analysis 3.3. Comparison 3 Diet and exercise counselling vs standard/other care, Outcome 3 Low weight gain.	206
Analysis 3.4. Comparison 3 Diet and exercise counselling vs standard/other care, Outcome 4 Preterm birth.	207
Analysis 3.5. Comparison 3 Diet and exercise counselling vs standard/other care, Outcome 5 Pre-eclampsia.	208
Analysis 3.6. Comparison 3 Diet and exercise counselling vs standard/other care, Outcome 6 Caesarean delivery.	209
Analysis 3.7. Comparison 3 Diet and exercise counselling vs standard/other care, Outcome 7 Macrosomia (Infant birthweight > 4000 g).	210
Analysis 4.1. Comparison 4 Exercise vs standard/other care, Outcome 1 Excessive weight gain.	212
Analysis 4.2. Comparison 4 Exercise vs standard/other care, Outcome 2 Weight gain (kg).	213
Analysis 4.3. Comparison 4 Exercise vs standard/other care, Outcome 3 Low weight gain.	214
Analysis 4.4. Comparison 4 Exercise vs standard/other care, Outcome 4 Preterm birth.	215
Analysis 4.5. Comparison 4 Exercise vs standard/other care, Outcome 5 Pre-eclampsia.	216
Analysis 4.6. Comparison 4 Exercise vs standard/other care, Outcome 6 Caesarean delivery.	217
Analysis 4.7. Comparison 4 Exercise vs standard/other care, Outcome 7 Macrosomia (Infant birthweight > 4000 g).	218
Analysis 5.1. Comparison 5 Diet and supervised exercise vs standard/other care, Outcome 1 Excessive weight gain.	219
Analysis 5.2. Comparison 5 Diet and supervised exercise vs standard/other care, Outcome 2 Weight gain (kg).	220
Analysis 5.3. Comparison 5 Diet and supervised exercise vs standard/other care, Outcome 3 Low weight gain.	221
Analysis 5.4. Comparison 5 Diet and supervised exercise vs standard/other care, Outcome 4 Pre-eclampsia.	221
Analysis 5.5. Comparison 5 Diet and supervised exercise vs standard/other care, Outcome 5 Caesarean delivery.	222
Analysis 5.6. Comparison 5 Diet and supervised exercise vs standard/other care, Outcome 6 Macrosomia (Infant birthweight > 4000 g).	223
Analysis 6.1. Comparison 6 Diet counselling/other vs standard/other care, Outcome 1 Excessive weight gain.	224
Analysis 6.2. Comparison 6 Diet counselling/other vs standard/other care, Outcome 2 Weight gain (kg).	225
Analysis 6.3. Comparison 6 Diet counselling/other vs standard/other care, Outcome 3 Low weight gain.	226
Analysis 6.4. Comparison 6 Diet counselling/other vs standard/other care, Outcome 4 Preterm birth.	226
Analysis 6.5. Comparison 6 Diet counselling/other vs standard/other care, Outcome 5 Pre-eclampsia.	227
Analysis 6.6. Comparison 6 Diet counselling/other vs standard/other care, Outcome 6 Caesarean delivery.	228
Analysis 6.7. Comparison 6 Diet counselling/other vs standard/other care, Outcome 7 Macrosomia (Infant birthweight > 4000 g).	229
ADDITIONAL TABLES	229
APPENDICES	252
WHAT'S NEW	255
HISTORY	255
CONTRIBUTIONS OF AUTHORS	256
DECLARATIONS OF INTEREST	256
SOURCES OF SUPPORT	256
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	256
INDEX TERMS	257

Diet or exercise, or both, for preventing excessive weight gain in pregnancy

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ABSTRACT

Background

This is an update of a Cochrane review first published in 2012, Issue 4. Excessive weight gain during pregnancy is associated with poor maternal and neonatal outcomes including gestational diabetes, hypertension, caesarean section, macrosomia, and stillbirth. Diet or exercise interventions, or both, may reduce excessive gestational weight gain (GWG) and associated poor outcomes; however, evidence from the original review was inconclusive.

Objectives

To evaluate the effectiveness of diet or exercise, or both, interventions for preventing excessive weight gain during pregnancy and associated pregnancy complications.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (5 November 2014), contacted investigators of the previously identified ongoing studies and scanned reference lists of retrieved studies.

Selection criteria

Randomised controlled trials (RCTs) of diet or exercise, or both, interventions for preventing excessive weight gain in pregnancy.

Data collection and analysis

Two review authors independently assessed trials for inclusion and risk of bias, extracted data and checked them for accuracy. We organised RCTs according to the type of interventions and pooled data using the random-effects model in the Review Manager software. We also performed subgroup analyses according to the initial risk of adverse effects related to poor weight control. We performed sensitivity analysis to assess the robustness of the findings.

Main results

We included 65 RCTs, out of which 49 RCTs involving 11,444 women contributed data to quantitative meta-analysis. Twenty studies were at moderate-to-high risk of bias. Study interventions involved mainly diet only, exercise only, and combined diet and exercise interventions, usually compared with standard care. Study methods varied widely; therefore, we estimated the average effect across studies and performed sensitivity analysis, where appropriate, by excluding outliers and studies at high risk of bias.

Diet or exercise, or both, interventions reduced the risk of excessive GWG on average by 20% overall (average risk ratio (RR) 0.80, 95% confidence interval (CI) 0.73 to 0.87; participants = 7096; studies = 24; $I^2 = 52\%$). This estimate was robust to sensitivity analysis, which reduced heterogeneity, therefore we graded this evidence as high-quality. Interventions involving low glycaemic load diets, supervised or unsupervised exercise only, or diet and exercise combined all led to similar reductions in the number of women gaining excessive weight in pregnancy.

Women receiving diet or exercise, or both interventions were more likely to experience low GWG than those in control groups (average RR 1.14, 95% CI 1.02 to 1.27; participants = 4422; studies = 11; $I^2 = 3\%$; *moderate-quality evidence*). We found no difference between intervention and control groups with regard to pre-eclampsia (RR 0.95, 95% CI 0.77 to 1.16; participants = 5330; studies = 15; $I^2 = 0\%$; *high-quality evidence*); however, maternal hypertension (not a pre-specified outcome) was reduced in the intervention group compared with the control group overall (average RR 0.70, 95% CI 0.51 to 0.96; participants = 5162; studies = 11; $I^2 = 43\%$; *low-quality evidence*).

There was no clear difference between groups with regard to caesarean delivery overall (RR 0.95, 95% CI 0.88 to 1.03; participants = 7534; studies = 28; $I^2 = 9\%$; *high-quality evidence*); although the effect estimate suggested a small difference (5%) in favour of the interventions. In addition, for combined diet and exercise counselling interventions there was a 13% (-1% to 25%) reduction in this outcome (borderline statistical significance).

We found no difference between groups with regard to preterm birth overall (average RR 0.91, 95% CI 0.68 to 1.22; participants = 5923; studies = 16; $I^2 = 16\%$; *moderate-quality evidence*); however limited evidence suggested that these effect estimates may differ according to the types of interventions, with a trend towards an increased risk for exercise-only interventions.

We found no clear difference between intervention and control groups with regard to infant macrosomia (average RR 0.93, 95% CI 0.86 to 1.02; participants = 8598; studies = 27; $I^2 = 0\%$; *high-quality evidence*), although the effect estimate suggested a small difference (7% reduction) in favour of the intervention group. The largest effect size occurred in the supervised exercise-only intervention group (RR 0.81, 95% CI 0.64 to 1.02; participants = 2445; studies = 7; $I^2 = 0\%$), which approached statistical significance ($P = 0.07$). Furthermore, in subgroup analysis by risk, high-risk women (overweight or obese women, or women with or at risk of gestational diabetes) receiving combined diet and exercise counselling interventions experienced a 15% reduced risk of infant macrosomia (average RR 0.85, 95% CI 0.73 to 1.00; participants = 3252; studies = nine; $I^2 = 0$; $P = 0.05$; *moderate-quality evidence*).

There were no differences in the risk of poor neonatal outcomes including shoulder dystocia, neonatal hypoglycaemia, hyperbilirubinaemia, or birth trauma (all *moderate-quality evidence*) between intervention and control groups; however, infants of high-risk women had a reduced risk of respiratory distress syndrome if their mothers were in the intervention group (RR 0.47, 95% CI 0.26 to 0.85; participants = 2256; studies = two; $I^2 = 0\%$; *moderate-quality evidence*).

Authors' conclusions

High-quality evidence indicates that diet or exercise, or both, during pregnancy can reduce the risk of excessive GWG. Other benefits may include a lower risk of caesarean delivery, macrosomia, and neonatal respiratory morbidity, particularly for high-risk women receiving combined diet and exercise interventions. Maternal hypertension may also be reduced. Exercise appears to be an important part of controlling weight gain in pregnancy and more research is needed to establish safe guidelines. Most included studies were carried out in developed countries and it is not clear whether these results are widely applicable to lower income settings.

PLAIN LANGUAGE SUMMARY

Diet and exercise interventions for preventing excessive weight gain during pregnancy

The issue

Diet or exercise, or both, for preventing excessive weight gain in pregnancy (Review)
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A large proportion of women gain more weight than is recommended during pregnancy. Excessive weight gain in pregnancy is associated with complications such as diabetes, high blood pressure, caesarean section, and large babies. This review aimed to determine whether diet or exercise measures, or both, could prevent excessive gestational weight gain (GWG), and if they were safe.

How we conducted the review

This is an update of a review first published in 2012 and is current to November 2014 and included randomised controlled trials (RCTs) only in the updated review. We grouped studies according to the types of interventions, and according to the types of participants, i.e. normal weight women (the low-risk group), all pregnant women (the mixed-risk group), and overweight or obese women, or women with or at risk of gestational diabetes (the high-risk group).

Findings

We included 65 randomised controlled trials, of which 49 trials involving 11,444 women contributed data. Twenty studies were at a moderate-to high-risk of bias. The diets tested were low sugar (low glycaemic load), diabetic, low-calorie or low-fat diets, with or without food diaries and regular weighing. The exercise interventions were most often of moderate intensity and involving regular walking, dance or aerobic classes. The comparison or control group generally received standard care. Overall, weight management interventions led to a reduction in the number of women gaining excess weight by a fifth (20%; range 13% to 27%) over the pregnancy. We considered this evidence to be high-quality.

Overall, we found no clear benefits of all diet or exercise interventions, or both, on other outcomes including pre-eclampsia, caesarean section, preterm birth, and having a baby weighing more than 4 kg (macrosomia), although we could not rule out a small effect on caesarean section (5% reduction) and macrosomia (7% reduction), particularly for women receiving combined diet and exercise counselling interventions. There was a tendency for supervised exercise-only interventions to reduce macrosomia too. Maternal hypertension (high blood pressure) was also reduced with the interventions. We found no clear differences between study groups with regard to most infant complications, except that for high-risk women the babies born to the women in the intervention group were less likely to experience breathing difficulties (respiratory distress syndrome) than babies in the control group. This evidence was mostly of a moderate quality.

The studies had differences in the types of interventions, types of participants (for example in terms of body mass index (BMI), number of previous pregnancies and age), delivery of the intervention (whether the intervention was incorporated into antenatal visits or delivered separately by a dietician), timing of the measurements, timing of commencement of the intervention (first, second or third trimester), the intensity of the intervention, and how it was monitored or supervised. Most included studies were carried out in developed countries and it is not clear whether these results are widely applicable to lower income settings.

Conclusions

We found high-quality evidence that diet or exercise interventions, or both, help to reduce excessive weight gain in pregnancy. They may also reduce caesarean deliveries, especially with combined diet and exercise interventions, and maternal hypertension. In addition, the chances of having a baby over 4 kg and the chances of the newborn having breathing difficulties after birth may be reduced, especially in overweight and obese women. Moderate-intensity exercise appears to be an important part of weight-control strategies in pregnancy; however, more research is needed on side-effects to inform safe guidelines.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

All diet and/or exercise interventions compared to standard/other care for preventing excessive weight gain in pregnancy						
Patient or population: pregnant women Settings: antenatal care settings Intervention: all diet and/or exercise interventions Comparison: routine care or minimal interventions (e.g. brochures)						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard/other care	All diet and/or exercise interventions				
Excessive weight gain	Study population		RR 0.80 (0.73 to 0.87)	7096 (24 RCTs)	⊕⊕⊕⊕ HIGH ¹	
	453 per 1000	362 per 1000 (330 to 394)				
Mean GWG (kg)			Mean difference not es- timated			Due to substantial het- erogeneity among stud- ies, we did not consider the pooled estimate to be meaningful. Limited subgroup analyses sug- gested that effect esti- mates might differ ac- cording to risk group
Low weight gain	Study population		RR 1.14 (1.02 to 1.27)	4422 (11 RCTs)	⊕⊕⊕○ MODERATE ²	
	227 per 1000	259 per 1000 (232 to 288)				

Preterm birth	Study population		RR 0.91 (0.68 to 1.22)	5923 (16 RCTs)	⊕⊕⊕○ MODERATE ³
	57 per 1000	52 per 1000 (39 to 70)			
Pre-eclampsia	Study population		RR 0.95 (0.77 to 1.16)	5330 (15 RCTs)	⊕⊕⊕⊕ HIGH
	66 per 1000	62 per 1000 (50 to 76)			
Caesarean delivery	Study population		RR 0.95 (0.88 to 1.03)	7534 (28 RCTs)	⊕⊕⊕⊕ HIGH
	288 per 1000	274 per 1000 (254 to 297)			
Macrosomia Infant birthweight > 4000 g	Study population		RR 0.93 (0.86 to 1.02)	8598 (27 RCTs)	⊕⊕⊕⊕ HIGH
	178 per 1000	166 per 1000 (153 to 182)			

*The basis for the **assumed risk** was the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹Although heterogeneity was moderate-to-high ($I^2 = 52\%$), the RR was robust to sensitivity analysis, which was associated with less heterogeneity ($I^2 = 40\%$), therefore we did not downgrade this evidence

²Downgraded due to imprecision of results according to types of intervention (-1)

³Downgraded due to risk of bias concerns and concerns that data could not be included in the analysis due to studies excluding women with or at risk of preterm birth post-randomisation from analysis (Cordero 2014; Di Carlo 2014; Murtezani 2014; Rauh 2013). This omission might have led to publication bias in the review's 'preterm birth' outcome (-1)

BACKGROUND

Description of the condition

Pregnancy weight gain guidelines

In 2009, the Institute of Medicines (IOM) in the United States updated earlier guidelines on weight gain during pregnancy (Medicine 1990; Medicine 2009). The report set out specific ranges of weight gain for women with different prepregnancy weights: suggesting that underweight women (body mass index (BMI) less than 18.5 kg/m²) gain 28 lbs to 40 lbs (12.5 kg to 18 kg); normal weight women (BMI 18.5 kg/m² to 24.9 kg/m²) gain 25 lbs to 35 lbs (11.5 kg to 16 kg); whereas overweight women (BMI 25 kg/m² to 29.9 kg/m²) were advised to gain between 15 lbs and 25 lbs (7 kg to 11.5 kg) and obese women (BMI at least 30 kg/m²) to gain between 11 lbs and 20 lbs (5 kg to 9 kg) (Medicine 2009).

Previous guidelines from the IOM (Medicine 1990) had been widely adopted but not universally accepted. However, a review of relevant information confirmed that pregnancy weight gain within the IOM's recommended ranges was associated with the best outcomes for both mothers and infants, and that weight gain within the IOM's recommended ranges is not harmful for the mothers or for their infants (Abrams 2000).

No official recommendations or clinical guidelines for weight gain during pregnancy exist in the United Kingdom (UK) (Ford 2001). However, a report from the UK Centre for Maternal and Child Enquiries (CMACE 2010) suggested a more comprehensive guidance for the care of overweight and obese women, and recommended weighing women in the third trimester and again when women are admitted in labour. Guidelines in other countries have also recommended monitoring weight gain in pregnancy. In Sweden, it has been recommended that the optimal gestational weight gain for Swedish women is 4 kg to 10 kg for BMI less than 20, 2 kg to 10 kg for BMI 20 to 24.9; less than 9 kg for women with a BMI of 25 to 29.9, and less than 6 kg for women with a BMI of 30 or more (Cedergren 2007). Maternal weight gain recommendations based on data from high-income countries may not be applicable to Asian women, who appear to have lower weight gains compared with women in Europe and North America (Abrams 1995; Siega-Riz 1993). Weight gain limits for Chinese women, taking ethnic-specific differences into account, have been recommended as 13 kg to 16.7 kg, 11 kg to 16.4 kg, and 7.1 kg to 14.4 kg respectively for women of low (BMI less than 19), moderate (BMI 19 to 23.5), and high (BMI greater than 23.5) BMI (Wong 2000).

Trends in pregnancy weight gain

Although the 1990 IOM guidelines have now been promoted for two decades it has been estimated that over this time only

30% to 40% of pregnant women in the United States gain gestational weight within the IOM recommended ranges (Abrams 2000; Cogswell 1999; Medicine 1990; Olson 2003). Furthermore, gestational weight gain above the guidelines is more common than gestational weight gain below (Stotland 2006). Several studies on gestational weight gain in the USA and Europe indicate that about 20% to 40% of women are gaining weight above the recommendations (Cedergren 2006; Medicine 2009; Olson 2003) and the prevalence of excessive gestational weight gain is increasing (Abrams 2000; Rhodes 2003; Schieve 1998). A retrospective cohort study undertaken to examine the trend in weight gain during pregnancy of 1,463,936 women over 16 years in North Carolina found that the proportion of women gaining excessive gestational weight (more than 18 kg) increased from 15.5% in 1988 to 19.5% in 2003; an additional 40 women per 1000 gained excessive weight by 2003 (Helms 2006). The recent IOM report summarised the situation in a number of countries; compared with two decades earlier "Women today are also heavier; a greater percentage of them are entering pregnancy overweight or obese, and many are gaining too much weight during pregnancy" (Medicine 2009).

Weight gain during pregnancy is generally inversely proportional to prepregnancy weight category. Although underweight women are least likely to exceed weight gain recommendations, obese women tend to gain less weight than normal and overweight women (Abrams 1989; Bianco 1998; Edwards 1996; Walling 2006). Two large population-based studies, in Sweden and the United States, found that approximately 30% of average and overweight women had high-gestational weight gain, compared with 20% of obese women (Cedergren 2006; Cogswell 1995).

Pregnancy weight gain and outcomes for mothers and infants

It is well known from large studies in a number of countries that excessive weight gain during pregnancy is associated with multiple maternal and neonatal complications. Retrospective cohort studies have examined the relationship between gestational weight gain and adverse neonatal outcomes among infants born at term. Gestational weight gain above the upper limit of the IOM guideline has been associated with a low five-minute Apgar score, seizure, hypoglycaemia, polycythaemia, meconium aspiration syndrome and large-for-gestational age compared with women within weight gain guidelines (Hedderson 2006; Stotland 2006). For obese women, low-gestational weight gain has been shown to decrease the risk of several undesirable outcomes including pre-eclampsia, caesarean section, instrumental delivery, and large-for-gestational-age births; whereas, excessive weight gain increased the risk for caesarean delivery in all maternal BMI classes (Cedergren 2006).

Findings from a national study in the UK revealed that compared with pregnant women in general, obese pregnant women were at increased risk of having a co-morbidity diagnosed before or dur-

ing pregnancy (in particular pregnancy-induced hypertension and gestational diabetes), were at increased risk of having induction of labour and a caesarean birth, were more likely to have postpartum haemorrhage, and their babies were at increased risk of stillbirth, neonatal death, of being large-for-gestational age and more likely to be admitted for special care (CMACE 2010).

A number of studies have concluded that excessive gestational weight gain increases postpartum weight retention (Gunderson 2000; Keppel 1993; Polley 2002; Rooney 2002; Rossner 1997; Scholl 1995) and is related to a two- to three-fold increase in the risk of becoming overweight after delivery (Gunderson 2000). Moreover, mothers who gained more weight during pregnancy have been shown to have children at higher risk of being overweight in early childhood (Oken 2007).

Description of the intervention

Pregnancy may be an optimal time to inform and challenge women to change their eating habits and physical activities, and thereby prevent excessive weight gain. Dietary control, exercise and eating behaviour modification are the main elements for controlling weight. Dietary interventions include low glycaemic, energy-restricted, diabetic, healthy eating, low carbohydrate and other diets. Regular exercise is an important part of a healthy lifestyle and most guidelines support moderate-intensity physical activity during pregnancy (Evenson 2014).

How the intervention might work

Diet and exercise interventions are recommended components of weight control programs in the general population. Diet interventions work mainly by limiting energy intake, whereas exercise interventions work by using energy. If one utilises more energy than one takes in, one creates an energy deficit, which facilitates the use of stored energy.

Why it is important to do this review

Pregnancy results in dramatic physiological changes, with weight gain occurring as part of the normal pregnancy process. This normal occurrence and expectation of weight gain in pregnancy can make it difficult for a woman of any prepregnancy weight to maintain her weight within recommended limits. Thus, pregnancy is a time when women especially need clear guidance on how best to maintain a healthy weight, in a way that will be safe for both mother and baby. Given the increasing prevalence and negative consequences of excessive gestational weight gain, preventing excessive weight gain during pregnancy is becoming increasingly important. The previous version of this review found weak evidence to support diet and exercise interventions to reduce gestational weight gain; however, findings were inconsistent and interventions

heterogeneous. Despite this and another systematic review that included randomised and non-randomised studies (Thangaratinam 2012), it remains unclear which types of interventions will yield the best outcomes for mothers and their infants, and whether interventions work equally for all risk groups. Pregnancy offers an ideal opportunity to support women towards a healthier lifestyle; however, strategies for reducing weight gain in the non-pregnant population may not be suitable for use in pregnancy. The aim of this review was to determine whether diet or exercise interventions, or both, for preventing excessive weight gain are effective and safe in pregnancy and to stimulate further research in this field.

OBJECTIVES

To evaluate the effectiveness and safety of diet or exercise, or both, interventions for preventing excessive weight gain during pregnancy.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and cluster-RCTs. Quasi-RCTs were not eligible.

Types of participants

Pregnant women of any BMI. We considered studies recruiting women with normal BMIs to have a 'low risk' of weight-related complications at baseline, those recruiting women from the general population including women of any BMI to have a 'mixed-risk' status, and studies of overweight and/or obese women, or high-risk women, as defined by the investigators, to have a 'high-risk' status.

Types of interventions

Any diet or exercise, or both, intervention (e.g. healthy eating plan, low glycaemic diet, exercise intervention, health education, lifestyle counselling) compared with standard or routine care for preventing excessive weight gain in pregnancy. We organised our main comparison into different intervention types, as follows:

- diet counselling only versus routine care;
- diet and exercise counselling versus routine care;
- diet interventions (e.g. low glycaemic diet) versus routine care;

- exercise (supervised or unsupervised) interventions only versus routine care;
- diet and supervised exercise interventions versus routine care.

We defined diet as a special selection of food, or energy intake, to which a participant was restricted. Exercise interventions included any activity requiring physical effort, carried out to sustain or improve health and fitness.

Types of outcome measures

Primary outcomes

Excessive weight gain as defined by investigators.

Secondary outcomes

For the mothers

1. Weight gain.
2. Low weight gain as defined by investigators.
3. Preterm birth.
4. Preterm prelabour rupture of membranes.
5. Pre-eclampsia/eclampsia.
6. Hypertension (not prespecified).
7. Induction of labour.
8. Caesarean delivery.
9. Postpartum complication including postpartum haemorrhage, wound infection, endometritis, need for antibiotics, perineal trauma, thromboembolic disease, maternal death.
10. Behaviour modification outcomes: diet, physical activity.

For the newborns

1. Birthweight (not prespecified).
2. Birthweight greater than 4000 g or greater than the 90th centile for gestational age and infant sex (macrosomia).
3. Birthweight less than 2500 g or less than the 10th centile for gestational age and infant sex.
4. Complication related to macrosomia including hypoglycaemia, hyperbilirubinaemia, infant birth trauma (palsy, fracture, shoulder dystocia), respiratory distress syndrome.

Long-term health outcomes

1. Maternal weight retention postpartum.
2. Childhood weight.

Gestational diabetes, an important outcome of many interventions aimed at preventing excessive weight gain in pregnancy, is the primary outcome of separate Cochrane reviews ([Crane 2013](#); [Han 2012](#); [Tieu 2008](#)) and is therefore not included in this review.

Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (5 November 2014).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

Searching other resources

For this update, we also contacted investigators of the previously identified ongoing studies by email to enquire about any new or imminent publications.

We searched the reference lists of retrieved studies.

We did not apply any language or date restrictions.

Data collection and analysis

For methods used in the previous version of this review, *see* [Muktabhant 2012](#).

For this update, we used the following methods based on a standard template used by the Cochrane Pregnancy and Childbirth Group for assessing the reports that were identified as a result of the updated search.

Selection of studies

Two review authors (Benja Muktabhant (BM); Theresa Lawrie (TL)) independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any

disagreement through discussion or, if required, we consulted the third review author (Pisake Lumbiganon (PL)).

Data extraction and management

Using Microsoft Excel®, we designed a spreadsheet to collect study data and piloted it with two studies. Thereafter, two review authors (BM, TL) extracted data from included studies using the piloted form. We resolved discrepancies through discussion or, if required, we consulted a third review author (PL). Data were entered into Review Manager software (RevMan 2014) by one review author (TL) and checked for accuracy by another (BM).

For studies that reported results for obese and overweight women separately, we combined these data for the 'high-risk women' subgroup.

Assessment of risk of bias in included studies

Two review authors (BM, TL) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreement was resolved by discussion or by involving a third assessor (PL or Malinee Laopaiboon (ML)).

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we planned to re-include missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);

- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);

- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we had about other possible sources of bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we attempted to assess the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - see [Sensitivity analysis](#).

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratios with 95% confidence intervals.

Continuous data

We used the mean difference if outcomes were measured in the same way between trials. We used the standardised mean difference to combine trials that measured the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomised trials

We included cluster-randomised trials in the analyses along with individually-randomised trials provided that cluster-RCT data were adjusted for clustering and any baseline imbalances. We considered it reasonable to combine the results from both if there was little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit was considered to be unlikely. We assessed risk of bias of these trials with particular attention to imbalances in baseline characteristics between the comparison arms, loss of clusters and appropriate analyses, and we acknowledged heterogeneity in the

randomisation unit, performing sensitivity analyses to investigate the effects of including these studies on review findings.

Other issues

For studies that included three arms, we divided the control group into two equal groups and considered each comparison separately. If the number of events in the control group was an odd number, to reduce the risk of overestimating effects in favour of the intervention group, we halved it and rounded it down; for odd denominators (total number of participants in the control group), we rounded these numbers upwards for the same reason.

Dealing with missing data

For included studies, we noted levels of attrition. We imputed data for studies where results were incompletely reported, e.g. if percentages and denominators were known, but the number of events was missing. For all outcomes, we carried out, as far as possible, analyses on an intention-to-treat basis, that is, we attempted to include all participants randomised to each group in the analyses. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau^2 , I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if an I^2 was greater than 30% and either a Tau^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity. If we identified heterogeneity above 30%, we explored it by sensitivity and subgroup analyses.

Assessment of reporting biases

Where there were 10 or more studies in the meta-analysis, we investigated reporting biases (such as publication bias) using funnel plots, which we assessed visually for asymmetry. If asymmetry was suggested by a visual assessment, we performed exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014). We used random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average of the range of possible treatment effects and we considered the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we did not combine trials. The results of these random-effects analyses are presented as the average

treatment effect with 95% confidence intervals and estimates of I^2 .

Subgroup analysis and investigation of heterogeneity

Subgroup analyses according to risk were not specified in the original review protocol. We conducted subgroup analyses according to the risk of adverse effects related to poor weight control with the high-risk group comprising only overweight and obese women, or women with or at risk of diabetes mellitus; a mixed-risk group comprising women in the general population, including women of any body mass indices (BMIs), and a low-risk group comprising normal weight women or women with BMIs of less than 25 kg/m². Where possible, we performed subgroup analysis for the following outcomes.

1. Excessive gestational weight gain (GWG)
2. Mean GWG
3. Low GWG
4. Preterm birth
5. Caesarean section
6. Pre-eclampsia
7. Macrosomia

For these analyses, we assessed subgroup differences by interaction tests available within RevMan (RevMan 2014) and reported the results of subgroup analyses quoting the χ^2 statistic and P value, and the interaction test I^2 value.

We explored heterogeneity by organising studies within comparisons according to the types of interventions.

Sensitivity analysis

We carried out sensitivity analyses to explore the effect of trial quality by excluding studies with risk of bias concerns from the analyses in order to assess whether this made any difference to the overall result.

Quality of evidence

Following meta-analysis, the quality of the evidence was assessed using the GRADE approach (Schunemann 2009) for the following key outcomes.

1. Excessive GWG
2. Mean GWG
3. Low GWG
4. Preterm birth
5. Caesarean section
6. Pre-eclampsia
7. Macrosomia

'Summary of findings' tables were created using this feature in RevMan 2014 with a summary of the intervention effect and a measure of quality produced for each of the above outcomes using the GRADE approach (GRADE 2014). The GRADE approach uses five considerations to assess the quality of the body of evidence for each outcome. We downgraded the evidence from 'high

quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

RESULTS

Description of studies

See [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#); [Characteristics of ongoing studies](#).

Results of the search

The original search identified 63 potential studies, of which we included 28 and excluded 12 studies in the original review (Muktabhant 2012). Two studies remained unclassified and 21 studies were ongoing.

Searches updated to November 2014 identified 169 eligible records. Of these 169 records, we included 102 records (pertaining to 41 new RCTs), and excluded 19 records (pertaining to 10 new studies, and one previously excluded study). Twelve of the 169 records were new reports of five previously included RCTs (Barakat 2011; Callaway 2010; Laitinen 2009; Luoto 2011; Phelan 2011), 36 records were of ongoing RCTs, and one record remained unclassified for this update (requiring translation from Farsi).

For this update, we excluded two previously included quasi-RCTs (Bechtel-Blackwell 2002; Moses 2006) and two RCTs that involved anti-suppressant drugs (Boileau 1968; Silverman 1971), which had previously been included under a broader title (see [Differences between protocol and review](#)).

Therefore, in summary, we included a total of 65 RCTs in this update (41 new and 24 previously included). Forty-nine studies (29 newly included) contributed data to quantitative synthesis. Twelve RCTs that had been identified as ongoing in the previous review have now been published, leaving 40 ongoing RCTs altogether (including new and previously included ongoing trials not yet reported) for this update ([Characteristics of ongoing studies](#)).

Included studies

Out of 65 included studies, two studies were cluster-RCTs (Luoto 2011; Rauh 2013); all other studies were RCTs. We were able to adjust data for one cluster-RCT (Luoto 2011; Appendix 1) and used adjusted data in meta-analyses, however we were unable to adjust data from Rauh 2013, which therefore did not contribute to meta-analyses. Seven RCT reports were conference abstracts (Angel 2011; Bisson 2014; Bogaerts 2012; Leiferman 2011; Marcinkevage 2012; Mujsindi 2014; Szmeja 2011). One of these

studies (Leiferman 2011), also generated a substudy in the form of a PhD thesis (Nodine 2011), which we have linked to this study in the references section. When reported in full, these seven RCTs may yet contribute data to future versions of this review; however, in general, we gleaned very little methodological information and no usable data from the abstracts. We have included information about these trials in the [Characteristics of included studies](#) tables, but they are not otherwise discussed in the sections below.

Participants

Two studies (Bogaerts 2012; Leiferman 2011) did not report the number of participants. The remaining 63 included studies involved at least 13,523 pregnant participants, and the number of participants in each study ranged from 12 (Magee 1990) to more than 2000 (Dodd 2014). Fifty-five out of 65 studies reported age and body mass index (BMI) at baseline and these were similar between study and control groups, with a few exceptions (see [Risk of bias in included studies](#)). Four studies recruited only nulliparous women (Althuisen 2013; Haakstad 2011; Murtezani 2014; Pinzon 2012). Most studies recruited women less than 20 weeks' gestation (48/65; 74%), with 27/65 (42%) studies recruiting women less than or equal to 14 weeks' gestation. Thirteen studies recruited participants after 20 weeks' gestation, namely Rhodes 2010 (13 to 28 weeks); Ferrara 2011 (approximately 31 weeks on average); Louie 2011 (20 to 32 weeks); Angel 2011 (more than 20 weeks); Hui 2012, Hui 2006 and Jackson 2011 (up to 26 weeks); Magee 1990 (13 to 38 weeks); Moses 2009 (approximately 30 weeks on average); Pollak 2014 (up to 21 weeks); Stafne 2012 (18 to 22 weeks); Thornton 2009 (12 to 28 weeks); Vitolo 2011 (10 to 29 weeks). Gestation at recruitment was not clear for the remainder (Bogaerts 2012; Leiferman 2011; Mujsindi 2014; Quinlivan 2011).

Studies included participants of various weight categories with 'normal weight' generally defined as a BMI greater than 18 and less than 25 kg/m², 'overweight' was considered to be greater than or equal to 25 kg/m² and less than 30 kg/m², and 'obese' was considered to be a BMI of greater than or equal to 30 kg/m². Thirty-four studies recruited women from the 'general population' (i.e. of various BMIs) and the proportion of women with normal BMIs varied widely across study samples reporting this baseline characteristic, from 15% to 79% of participants. Most of these studies did not report results for high- (overweight/obese women) and low-risk (normal BMI) women separately; however, for eight of these studies (Althuisen 2013; Hui 2014; Jeffries 2009; Phelan 2011; Polley 2002; Ronnberg 2014; Ruiz 2013; Vitolo 2011), main outcomes were reported separately for women with low/normal versus overweight/obese prepregnancy weights; therefore, where possible, we used relevant data from these studies for meta-analyses pertaining to low, mixed-risk and high-risk groups. One study (ROLO 2012) recruited only secundigravida women who had previously given birth to a baby with macrosomia and reported certain outcomes separately for women in all weight categories.

Among 31 studies recruiting women in high-risk groups, 24 studies recruited overweight and obese women, or obese women only (Angel 2011; Bisson 2014; Bogaerts 2012; Callaway 2010; Dodd 2014; Guelinckx 2010; Kong 2014; Magee 1990; Marcinkevage 2012; Mujsindi 2014; Nascimento 2012; Oostdam 2012; Petrella 2013; Poston 2013; Pollak 2014; Quinlivan 2011; Renault 2014; Rhodes 2010; Santos 2005; Szmeja 2011; Thornton 2009; Vesco 2013; Vinter 2012; Wolff 2008); and seven recruited women with, or defined as at high risk of, gestational diabetes (Ferrara 2011; Harrison 2013; Korpi-Hyovalti 2011; Louie 2011; Luoto 2011; Moses 2009; Rae 2000).

Settings

Most studies were conducted in high-income countries, including Australia (Callaway 2010; Dodd 2014; Harrison 2013; Jeffries 2009; Louie 2011; Moses 2009; Moses 2014; Quinlivan 2011; Szmeja 2011; Wilkinson 2012), Belgium (Bogaerts 2012; Guelinckx 2010), Canada (Hui 2006; Hui 2012; Hui 2014; Hui 2014; Ruchat 2012), Denmark (Renault 2014; Vinter 2012; Wolff 2008), Finland (Korpi-Hyovalti 2011; Laitinen 2009; Luoto 2011), Germany (Rauh 2013), Ireland (ROLO 2012), Italy (Di Carlo 2014; Petrella 2013), Kosovo (Murtezani 2014), Norway (Haakstad 2011), Sweden (Petrov Fieril 2014; Ronnberg 2014), The Netherlands (Althuisen 2013; Oostdam 2012), Spain (Barakat 2011; Cordero 2014; Ruiz 2013), the United Kingdom (Poston 2013) and the United States of America (USA) (Angel 2011; Asbee 2009; Bisson 2014; Clapp 2002a; Clapp 2002b; Ferrara 2011; Hawkins 2014; Kieffer 2014; Kong 2014; Leiferman 2011; Magee 1990; Marcinkevage 2012; Mujsindi 2014; Phelan 2011; Pollak 2014; Polley 2002; Price 2012; Rhodes 2010; Thornton 2009; Vesco 2013). Two of these studies (Hui 2006; Polley 2002) recruited women with low-, or low-middle incomes in Canada and the USA, respectively. Of the six studies conducted in low-income countries, four were conducted in Brazil (De Oliveria Melo 2012; Nascimento 2012; Santos 2005; Vitolo 2011), one was conducted in Columbia (Pinzon 2012) and one was conducted in Taiwan (Huang 2011).

Interventions

All the interventions considered in this review included modifying or restricting diet or increasing exercise, or both; however there was considerable variation in the interventions used, which included:

- diet only (eight studies): low glycaemic load (GL) diet versus conventional healthy eating or routine or other care: Angel 2011; Clapp 2002a; Louie 2011; Moses 2009; Moses 2014; Rhodes 2010; ROLO 2012; one study evaluated a supervised low calorie diet (Magee 1990);
- diet and exercise counselling (25 studies): Asbee 2009; Althuisen 2013; Bogaerts 2012; Dodd 2014; Ferrara 2011; Guelinckx 2010; Harrison 2013; Hawkins 2014; Huang 2011; Jackson 2011; Kieffer 2014; Korpi-Hyovalti 2011; Luoto 2011;

Marcinkevage 2012; Mujsindi 2014; Petrella 2013; Phelan 2011; Pollak 2014; Polley 2002; Quinlivan 2011; Rauh 2013; Renault 2014; Szmaja 2011; Vesco 2013; Wilkinson 2012;

- exercise interventions (e.g. supervised exercise, individualised exercise programs, dance classes, provision of pedometers or treadmills) (20 studies): Barakat 2011; Bisson 2014; Callaway 2010; Clapp 2002b; Cordero 2014; De Oliveria Melo 2012; Haakstad 2011; Kong 2014; Leiferman 2011; Murtezani 2014; Nascimento 2012; Oostdam 2012; Petrov Fieril 2014; Pinzon 2012; Poston 2013; Price 2012; Renault 2014; Ruiz 2013; Ronnberg 2014; Santos 2005;
- diet and supervised exercise interventions (five studies): Hui 2006; Hui 2012; Hui 2014; Ruchat 2012; Vinter 2012;
- diet counselling/other (seven studies): Di Carlo 2014; Jeffries 2009; Laitinen 2009; Rae 2000; Thornton 2009; Vitolo 2011; Wolff 2008.

Interventions varied in intensity. Control groups mostly comprised routine or standard care (which also varied considerably in different settings and was not always well-described). Hui 2006 compared a supervised group exercise and diet intervention with an exercise and diet information pack. Clapp 2002b compared different exercise intensities at different stages of pregnancy. Some studies included more than two arms (De Oliveria Melo 2012; Laitinen 2009; Guelinckx 2010; Renault 2014).

Outcomes

Gestational weight gain (GWG) or excessive GWG, or both, were reported as primary or secondary outcomes in 75% of included studies. Excessive GWG was usually defined according to prevailing IOM guidelines. Generally, baseline weight was measured at recruitment; however, several studies used self-reported prepregnancy weight as the baseline measurement (e.g. Di Carlo 2014; Haakstad 2011; Hui 2012; Louie 2011; Moses 2014; Oostdam 2012). The final weight measurement was either collected by researchers at the last clinic or hospital visit (usually greater than or equal to 36 weeks) or from medical records. Several studies collected these follow-up weight data earlier than 36 weeks, including Vesco 2013 (34 weeks), Oostdam 2012 (32 weeks), Harrison 2013 (28 weeks), and Petrov Fieril 2014 (25 weeks). The latter study included mean weight as an outcome, but not mean weight gain.

Other reported outcomes included postpartum weight retention, macrosomia, infant birthweight, gestational diabetes, pre-eclampsia/hypertension, diet and physical activity (PA) behaviour, breastfeeding, biochemical parameters, e.g. serum insulin levels, and various other maternal and neonatal outcomes.

Excluded studies

Initially, we excluded 26 studies (12 previously excluded, 10 new excluded and four previously included). One previously excluded study (Moses 2007), was a follow-up of a previously included study (Moses 2006) and these two reports are now listed together, reducing the number of excluded studies to 25 studies. The main reasons for exclusion were as follows.

1. Non-randomised study or quasi-RCT: Bechtel-Blackwell 2002; Breslow 1963; Daley 2014; Davenport 2011; Graham 2014; Gray-Donald 2000; Kinnunen 2007; Maitland 2014; Mohebi 2009; Moses 2006; Mottola 2010; Olson 2004; Stutzman 2010; Walker 1966.
2. Participants included non-pregnant or postpartum women: Campbell 2004; Faucher 2008; Hausenblas 2008; Te Morenga 2011; Wisner 2006.
3. Not a diet or exercise intervention: Asemi 2011; Boileau 1968; Hauner 2012; Ismail 1990; Lindsay 2014; Silverman 1971.

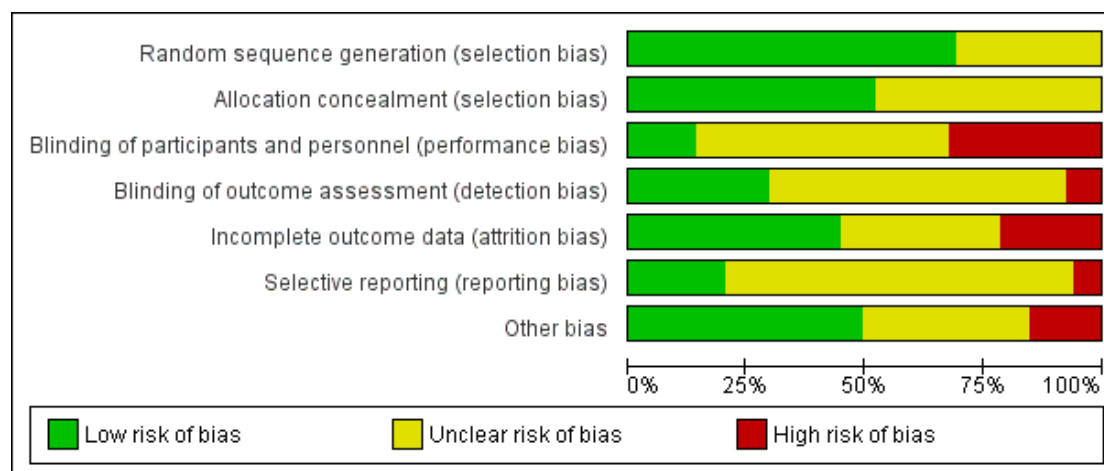
Risk of bias in included studies

Details of the methodological quality of each study are given in *Characteristics of included studies*, Figure 1, and Figure 2. Studies were considered to be potentially at a moderate-to-high risk of bias if they were assessed to be at 'high risk' for at least one of the risk of bias items below, excluding blinding, as most studies were open-label. We considered 35/65 studies (54%) to be at a low risk of bias overall, and 20/65 (29%) to be at a moderate-to-high risk of bias overall (Asbee 2009; Barakat 2011; Callaway 2010; Cordero 2014; Di Carlo 2014; Ferrara 2011; Luoto 2011; Murtezani 2014; Nascimento 2012; Oostdam 2012; Petrov Fieril 2014; Pinzon 2012; Price 2012; Rauh 2013; Ruchat 2012; Santos 2005; Stafne 2012; Vitolo 2011; Wilkinson 2012; Wolff 2008). Five of the latter studies (Callaway 2010; Pinzon 2012; Rauh 2013; Vitolo 2011; Wilkinson 2012) did not contribute to quantitative analysis in this update. The remaining 10 studies were at an unclear risk of bias (Angel 2011; Bisson 2014; Bogaerts 2012; Korpi-Hyovalti 2011; Leiferman 2011; Magee 1990; Marcinkevage 2012; Mujsindi 2014; Polley 2002; Szmaja 2011).

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Althuisen 2013	●	●	●	●	●	●	●
Angel 2011	●	●	●	●	●	●	●
Asbee 2009	●	●	●	●	●	●	●
Barakat 2011	●	●	●	●	●	●	●
Blissin 2014	●	●	●	●	●	●	●
Bogaerts 2012	●	●	●	●	●	●	●
Callaway 2010	●	●	●	●	●	●	●
Clapp 2002a	●	●	●	●	●	●	●
Clapp 2002b	●	●	●	●	●	●	●
Cordero 2014	●	●	●	●	●	●	●
De Oliveira Melo 2012	●	●	●	●	●	●	●
Di Carlo 2014	●	●	●	●	●	●	●
Dodd 2014	●	●	●	●	●	●	●
Ferrara 2011	●	●	●	●	●	●	●
Gustlinck 2010	●	●	●	●	●	●	●
Haakstad 2011	●	●	●	●	●	●	●
Harrison 2013	●	●	●	●	●	●	●
Hawkins 2014	●	●	●	●	●	●	●
Huang 2011	●	●	●	●	●	●	●
Hui 2008	●	●	●	●	●	●	●
Hui 2012	●	●	●	●	●	●	●
Hui 2014	●	●	●	●	●	●	●
Jackson 2011	●	●	●	●	●	●	●
Jeffries 2009	●	●	●	●	●	●	●
Kieffer 2014	●	●	●	●	●	●	●
Kong 2014	●	●	●	●	●	●	●
Korpi-Hyöväli 2011	●	●	●	●	●	●	●
Laitinen 2009	●	●	●	●	●	●	●
Letteman 2011	●	●	●	●	●	●	●
Louie 2011	●	●	●	●	●	●	●
Luro 2011	●	●	●	●	●	●	●
Magree 1990	●	●	●	●	●	●	●
Martinkavage 2012	●	●	●	●	●	●	●
Moses 2009	●	●	●	●	●	●	●
Moses 2014	●	●	●	●	●	●	●
Mujisindi 2014	●	●	●	●	●	●	●
Murtezani 2014	●	●	●	●	●	●	●
Nascimento 2012	●	●	●	●	●	●	●
Oostdam 2012	●	●	●	●	●	●	●
Petrella 2013	●	●	●	●	●	●	●
Petrov Fierli 2014	●	●	●	●	●	●	●
Phelan 2011	●	●	●	●	●	●	●
Pinzon 2012	●	●	●	●	●	●	●
Poliak 2014	●	●	●	●	●	●	●
Polley 2002	●	●	●	●	●	●	●
Positon 2013	●	●	●	●	●	●	●
Price 2012	●	●	●	●	●	●	●
Quintinan 2011	●	●	●	●	●	●	●
Rae 2000	●	●	●	●	●	●	●
Rauh 2013	●	●	●	●	●	●	●
Renault 2014	●	●	●	●	●	●	●
Rhodes 2010	●	●	●	●	●	●	●
ROLO 2012	●	●	●	●	●	●	●
Ronnberg 2014	●	●	●	●	●	●	●
Ruchat 2012	●	●	●	●	●	●	●
Ruz 2013	●	●	●	●	●	●	●
Santos 2005	●	●	●	●	●	●	●
Stafne 2012	●	●	●	●	●	●	●
Szmajda 2011	●	●	●	●	●	●	●
Thornston 2009	●	●	●	●	●	●	●
Vesco 2013	●	●	●	●	●	●	●
Vinter 2012	●	●	●	●	●	●	●
Vitolo 2011	●	●	●	●	●	●	●
Wilkinson 2012	●	●	●	●	●	●	●
Wolff 2008	●	●	●	●	●	●	●

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Allocation

Out of 65 studies, 45 (69%) were assessed as being at low risk of bias for generation of the randomisation sequence and 34 (52%) used methods that we judged to be at a low risk of bias for allocation concealment. The remaining studies (25%) were at an unclear risk of selection bias.

Blinding

Twenty-four out of 65 studies (37%) had taken some steps to implement performance or detection blinding, or both. Achieving participant and personnel blinding of treatment allocation for diet and exercise interventions was indicated to be not feasible in several studies and was not described in many others. Where studies were described as open-label or unblinded, we classified these as at a high risk of bias for this item; however, it was difficult to ascertain whether the lack of blinding, or unsuccessful blinding, impacted on outcomes or resulted in any systematic bias. In addition, the studies that did not describe blinding were probably unblinded. For these reasons we did not use blinding as a criterion in the overall assessment of individual study bias but rather took into account other types of bias.

Incomplete outcome data

We assessed 29/65 studies (45%) to be at a low risk of attrition bias. Fourteen studies (22%) (Callaway 2010; Cordero 2014; Di Carlo

2014; Ferrara 2011; Luoto 2011; Oostdam 2012; Petrov Fieril 2014; Pinzon 2012; Price 2012; Ruchat 2012; Santos 2005; Stafne 2012; Wilkinson 2012; Wolff 2008) had high attrition (greater than 20%) overall, or for the intervention or control group only, or for certain outcomes, and we considered these to be at a high risk of bias accordingly. In the remaining studies, loss of outcome data was either not stated or was less than 20% but there were other concerns (e.g. imbalance in attrition between arms) and for these we considered the risk of bias to be unclear.

Selective reporting

It was difficult to assess bias associated with the outcome reporting bias as we did not have access to the study protocols of most studies and we did not know whether results for all outcomes where data had been collected had been reported; we therefore assessed many of these studies as being unclear for the outcome reporting bias. However, we considered Cordero 2014 and Di Carlo 2014 to be at a potentially high risk of reporting bias as only per protocol findings were reported. During the course of these studies, women with preterm labour were excluded, therefore, this potential side-effect could not be evaluated. In addition, Cordero 2014 additionally excluded data from women with poor adherence to the intervention; therefore, the reported results may be biased in the direction of the intervention.

Other potential sources of bias

Six studies had important baseline imbalances in the characteristics of the women in the intervention and control groups (Barakat 2011; Cordero 2014; Di Carlo 2014; Price 2012; Rauh 2013; Santos 2005) that might have impacted the results in favour of the intervention. Barakat 2011, Cordero 2014, Di Carlo 2014 and Price 2012 did not adjust results for these imbalances and we therefore considered them to be at a potentially high risk of bias. Cordero 2014 additionally had an unexplained difference in intervention and control group sizes. Rauh 2013 is discussed below under 'Assessment of cluster-RCTs'.

In Price 2012, control participants were told not to exercise because it would blur the distinction between the groups. This contributed to high drop-out rates in the control group and bias in favour of the intervention, whilst making results less applicable by enforcing no exercise. Oostdam 2012 had issues with adherence to the intervention, which may have biased results in favour of the control group.

Most studies involving an exercise component excluded women at risk of miscarriage or preterm birth at screening. However, four studies excluded women with or at risk of preterm birth post-randomisation from analysis (Cordero 2014; Di Carlo 2014; Murtezani 2014; Rauh 2013). This omission might have led to publication bias in the review's 'preterm birth' outcome. Any other potential sources of bias were noted in the Characteristics of included studies.

Assessment of cluster-RCTs

Two trials were cluster-RCTs (Luoto 2011; Rauh 2013).

Recruitment bias: In Rauh 2013, intervention and control groups differed substantially in size as "During recruitment it turned out that it was easier to recruit women for the intervention group than for the control group, yielding a 2:1 ratio", instead of 1:1. In Luoto 2011, more than 20% and 30% in the intervention and control arms, respectively, were excluded from analysis based on oral glucose tolerance tests conducted between eight and 12 weeks' gestation. Only 40% and 47% of women in intervention and control groups, respectively, who were assessed as preliminary eligible were analysed.

Baseline imbalances: Baseline imbalances were limited to differences in educational levels between arms in Luoto 2011. However, in Rauh 2013, baseline characteristics differed significantly with regard to pregravid BMI ($P = 0.003$) and BMI at booking ($P = 0.008$), with a higher proportion of women in the control group considered obese or overweight (16.2% versus 31.4%; $P = 0.009$). In addition, mean age was younger and gestational age at booking was significantly earlier in the intervention clusters.

Loss of clusters: There was no loss of clusters in either study.

Analysis methods: Both Luoto 2011 and Rauh 2013 reported adjusting the summary effect size for clusters and baseline imbalances. However, outcome data for both studies needed to be esti-

mated for use in meta-analysis, and this was not possible for Rauh 2013, due to insufficient data and the lack of an intracluster correlation coefficient. The results reported in Rauh 2013 favoured the intervention arm for weight gain outcomes (Appendix 2), and although these were adjusted for BMI, age and clustering, there may also have been other (unknown) differences between the women in these groups. We therefore considered this study to be at potentially high risk of bias; however, Rauh 2013 data did not contribute to meta-analyses.

Comparability with individually-randomised trials: These trials were comparable to individually-randomised trials except that large differences in study group sizes occurred in Rauh 2013. Study investigators reported that the clusters (gynaecology practices) differed significantly in size; the result was that 227 versus 129 women were eligible for the intervention and control clusters, respectively.

Overall assessment: We assessed these cluster-RCTs as moderate-to-high risk of bias. Adjusted Luoto 2011 data were used in meta-analyses; however, Rauh 2013 data could not be adjusted and were therefore not used.

Effects of interventions

See: **Summary of findings for the main comparison** All diet and/or exercise interventions compared to standard/other care for preventing excessive weight gain in pregnancy; **Summary of findings 2** Comparative table of findings by intervention type

We compared diet or exercise, or both, interventions together (comparisons 1) organised by types of interventions (see Table 1 for the rationale for study categories). We also analysed each intervention category separately stratified for risk (comparisons 2, 3, 4, and 5) for all women (i.e. a mixed-risk population), low risk, and high-risk women.

1. Diet and/or exercise interventions vs routine care in all pregnant women

Forty-nine studies involving 11,444 participants contributed data to these analyses. A maximum of 36 studies contributed data to Comparison 1 analyses. Funnel plots were asymmetrical for most analyses.

1.1 Excessive gestational weight gain (GWG)

Diet or exercise, or both, interventions resulted in an average risk reduction of excessive GWG of 20% in favour of the intervention group (risk ratio (RR) 0.80, 95% confidence interval (CI) 0.73 to 0.87; participants = 7096; studies = 24; $I^2 = 52\%$; Analysis 1.1). Reductions in favour of the intervention arms were consistent across the different types of intervention groups, except for the heterogeneous group comprising 'diet counselling or other interventions', with the largest reduction occurring with 'supervised exercise and diet' interventions.

Sensitivity analysis

When we removed five studies with risk of bias concerns from the meta-analysis (Cordero 2014; Di Carlo 2014; Ferrara 2011; Hui 2006; Ruchat 2012), heterogeneity was reduced and the average overall effect in favour of the intervention group was robust to the original result (RR 0.82, 95% CI 0.76 to 0.89; participants = 6437; studies = 19; $I^2 = 40\%$). In addition, when we pooled data from exercise only interventions (supervised and unsupervised), findings were similar (RR 0.79, 95% CI 0.70 to 0.89; participants = 1901; studies = six; $I^2 = 0\%$).

Quality of the evidence

We graded this evidence as high quality.

1.2 Mean gestational weight gain (GWG)

Thirty-six studies reported this outcome; however, due to substantial heterogeneity we did not pool these data (Analysis 1.2). Thirteen studies reported significant differences in mean GWG between intervention and control groups in favour of the interventions, with five studies reporting mean differences in GWG in excess of 5 kg (Clapp 2002a; Di Carlo 2014; Thornton 2009; Quinlivan 2011; Wolff 2008). The remainder of studies found no significant difference in mean GWG between groups.

1.3 Low weight gain

Women in the intervention group were significantly more likely to experience low GWG compared with the control group (average RR 1.14, 95% CI 1.02 to 1.27; participants = 4422; studies = 11; $I^2 = 3\%$; Analysis 1.3). Results according to types of interventions were not statistically significant, with wide confidence intervals and a consistent trend in favour of the control group. However, when data from the supervised and unsupervised exercise groups were combined the effect was of borderline statistical significance (RR 1.19, 95% CI 1.00 to 1.41; participants = 1565; studies = four; $I^2 = 0\%$).

Sensitivity analysis

There were no serious risk of bias concerns for this analysis.

Quality of the evidence

We graded this evidence as moderate quality.

1.4 Preterm birth

There was no statistically significant difference between intervention and control groups for preterm birth outcomes (average RR 0.91, 95% CI 0.68 to 1.22; participants = 5923; studies = 16; $I^2 = 16\%$; Analysis 1.4). Point estimates for exercise only interventions favoured the control groups; however, when data from the supervised and unsupervised groups were combined the trend was not statistically significant (RR 1.59, 95% CI 0.76 to 3.33; participants = 1358; studies = five; $I^2 = 0\%$).

Sensitivity analysis

When two studies with risk of bias concerns were excluded from the analysis (Price 2012; Petrella 2013), results were similar to the original analysis (average RR 0.88, 95% CI 0.70 to 1.10; participants = 5800; studies = 14; $I^2 = 0\%$).

Quality of the evidence

We downgraded this evidence to moderate quality due to risk of bias concerns arising from potential under-reporting (in at least four studies, women at risk of preterm birth were withdrawn; see Risk of bias in included studies).

1.5 Pre-eclampsia

There was no statistically significant difference between the intervention and control groups with regard to pre-eclampsia (average RR 0.95, 95% CI 0.77 to 1.16; participants = 5330; studies = 15; $I^2 = 0\%$; Analysis 1.5).

Quality of the evidence

We graded the quality of this evidence as high.

1.6 Hypertension (not prespecified)

Maternal hypertension occurred significantly more frequently in the control group compared with the intervention group (average RR 0.70, 95% CI 0.51 to 0.96; participants = 5162; studies = 11; $I^2 = 43\%$; Analysis 1.6).

Sensitivity analysis and investigation of heterogeneity

When we excluded three studies (Petrella 2013; Price 2012; Stafne 2012) with risk of bias concerns, the result remained in favour of the interventions; however it was no longer statistically significant (RR 0.74, 95% CI 0.53 to 1.02; participants = 4314; studies = eight; $I^2 = 44\%$). Heterogeneity could not be attributed to differences between the different types of interventions. We investigated heterogeneity further below, by subgrouping studies by participant risk group.

Quality of the evidence

We downgraded the evidence to low quality due to inconsistency and risk of bias concerns.

1.7 Induction of labour

There was no statistically significant difference between intervention and control groups for this outcome (average RR 1.06, 95% CI 0.94 to 1.19; participants = 3832; studies = eight; $I^2 = 9\%$; [Analysis 1.7](#)).

Quality of the evidence

We graded the quality of this evidence as high.

1.8 Caesarean delivery

There was no statistically significant difference in the risk of caesarean section between intervention and control groups (average RR 0.95, 95% CI 0.88 to 1.03; participants = 7534; studies = 28; $I^2 = 9\%$; [Analysis 1.8](#)); although the point estimate favoured a small reduction in favour of the intervention group. Effect estimates for supervised and unsupervised exercise interventions only, alone or combined, were robust to the overall findings. However, for the diet and exercise counselling interventions, the effect estimate approached statistical significance with a 13% reduction in caesarean delivery in the intervention group (RR 0.87, 95% CI 0.75 to 1.01; participants = 3406; studies = 9; $I^2 = 15\%$; $P = 0.06$).

Sensitivity analysis

When we excluded two studies with risk of bias concerns ([Di Carlo 2014](#); [Price 2012](#)), the results moved further toward the null (average RR 0.97, 95% CI 0.91 to 1.04; participants = 7323; studies = 26; $I^2 = 2\%$).

Quality of the evidence

We graded the quality of this evidence as high, although effects may differ according to types of interventions.

1.9 and 1.10 Maternal postpartum weight retention (mean [kg] and rate)

Diet or exercise, or both, interventions on average were not associated with less postpartum weight retention in kilograms compared with the controls (average mean difference (MD) -1.12, 95% CI -2.49 to 0.25; participants = 818; studies = 7; $I^2 = 55\%$; [Analysis 1.9](#)); however, pooled data from five studies indicated significantly lower rates of postpartum weight retention in the intervention group (average RR 0.78, 95% CI 0.63 to 0.97; participants = 902; studies = five; $I^2 = 63\%$; [Analysis 1.10](#)).

Sensitivity analysis and investigation of heterogeneity

Time frames for these assessments ranged from six weeks to six months postpartum which may have accounted for the heterogeneity. Several studies had risk of bias concerns (mainly attrition bias) for these outcomes; therefore, we did not perform sensitivity analysis.

Quality of the evidence

We graded this evidence as low quality due to inconsistency and risk of bias concerns.

1.11 to 1.13 Behaviour modification outcomes (diet and physical activity)

Energy and fibre intake

Data on mean energy intake were available for 12 studies and revealed a statistically significant difference in energy intake (in kilojoules) between intervention and control groups (average MD -570.77, 95% CI -894.28 to -247.26; participants = 4065; studies = 12; $I^2 = 73\%$; [Analysis 1.11](#)). Similarly, fibre intake in grams was significantly higher in the intervention group (MD 1.53, 95% CI 0.94 to 2.12; participants = 3466; studies = 8; $I^2 = 0\%$; [Analysis 1.12](#)).

Physical activity score at 26 to 29 weeks

Women in the intervention group revealed higher physical activity scores on average compared with controls (average standardised mean difference (SMD) 0.40, 95% CI 0.18 to 0.61; participants = 2851; studies = 9; $I^2 = 75\%$; [Analysis 1.13](#)).

Quality of evidence

We graded evidence relating to behaviour modification outcomes as low quality due to heterogeneity and risk of bias concerns, particularly detection (mainly self-reported outcomes) and attrition bias.

1.14 Infant birthweight greater than 4000 g

There was no statistically significant difference in the risk of macrosomia (birthweight greater than 4000 g) between intervention and control groups overall (average RR 0.93, 95% CI 0.86 to 1.02; participants = 8598; studies = 27; $I^2 = 0\%$; [Analysis 1.14](#)), although the trend favoured the intervention groups. For the 'supervised exercise' intervention group, the effect in favour of the intervention bordered on statistical significance (average RR 0.81, 95% CI 0.64 to 1.02; participants = 2445; studies = seven; $I^2 = 0\%$; $P = 0.07$), but not when supervised and unsupervised exercise

interventions were combined (RR 0.87, 95% CI 0.71 to 1.07; participants = 2674; studies = nine; I^2 = 0%).

Sensitivity analysis

Results were similar when we performed sensitivity analysis by excluding seven studies (Cordero 2014; Ferrara 2011; Luoto 2011; Murtezani 2014; Stafne 2012; Ruchat 2012) with risk of bias concerns from the analysis (average RR 0.92, 95% CI 0.82 to 1.04; participants = 7021; studies = 20; I^2 = 11%).

Quality of the evidence

We graded the evidence as high, although further research may reveal important differences between intervention types.

1.15 Infant birthweight greater than 90th centile

There was no statistically significant difference in the risk of large-for-gestational-age infants between intervention and control groups (average RR 0.92, 95% CI 0.80 to 1.05; participants = 4525; studies = 18; I^2 = 0%; Analysis 1.15); however, the effect in the diet and exercise counselling group non-significantly favoured the intervention (RR 0.87, 95% CI 0.74 to 1.02; participants = 2777; studies = 6; I^2 = 0%).

Quality of the evidence

We graded the quality of this evidence as high.

1.16 Mean birthweight (g)

There was no statistically significant difference in mean birthweight between intervention and control groups (average MD 12.20, 95% CI -15.26 to 39.65; participants = 8350; studies = 29; I^2 = 44%; Analysis 1.16).

Sensitivity analysis and investigation of heterogeneity

There were many risk of bias concerns for this outcome (e.g. due to post-randomisation exclusions of women with preterm birth in several studies) but the overall result remained fairly robust to exclusion of high-risk studies.

Quality of the evidence

We graded the quality of the evidence as moderate due to inconsistency.

1.17 and 1.18 Infant birthweight less 2500 g or less than 10th centile

There was no statistically significant difference between groups with respect to birthweight less than 2500 g (average RR 0.88, 95% CI 0.67 to 1.14; participants = 4834; studies = 12; I^2 = 0%; Analysis 1.17) or small-for-gestational-age infants (average RR 1.09, 95% CI 0.61 to 1.94; participants = 662; studies = seven; I^2 = 0%, Analysis 1.18).

Quality of the evidence

We downgraded the quality of this evidence to moderate due to potential risk of bias concerns relating mainly to the limited reporting of this outcome.

1.19 Shoulder dystocia

There was no statistically significant difference in the risk of shoulder dystocia between intervention and control groups (average RR 1.02, 95% CI 0.57 to 1.83; participants = 3253; studies = four; I^2 = 8%, Analysis 1.19).

Quality of the evidence

We graded this evidence as moderate quality due to imprecision.

1.20 Neonatal hypoglycaemia

There was no statistically significant difference in the risk of neonatal hypoglycaemia between intervention and control groups (average RR 0.95, 95% CI 0.76 to 1.18; participants = 2601; studies = four; I^2 = 0%); Analysis 1.20).

Quality of the evidence

We graded this evidence as moderate quality due to indirectness (may not apply to all types of interventions).

1.21 Neonatal birth trauma

There was no statistically significant difference between intervention and control groups (average RR 0.89, 95% CI 0.35 to 2.30; participants = 2256; studies = two; I^2 = 0%; Analysis 1.21). Both included studies (Dodd 2014; Vesco 2013) were diet and exercise counselling interventions and were conducted in high-risk populations.

Quality of the evidence

We graded this evidence as moderate quality due to imprecision.

1.22 Neonatal hyperbilirubinaemia

There was no statistically significant difference between intervention and control groups (average RR 0.83, 95% CI 0.62 to 1.10; participants = 2256; studies = two; $I^2 = 0\%$; [Analysis 1.22](#)). Both included studies ([Dodd 2014](#); [Vesco 2013](#)) were diet and exercise counselling interventions and were conducted in high-risk populations.

Quality of the evidence

We graded this evidence as moderate quality due to indirectness (may not apply to all types of interventions).

1.23 Neonatal respiratory distress syndrome

Infants in the intervention group had a significantly reduced risk of experiencing respiratory distress than infants in the control group (average RR 0.47, 95% CI 0.26 to 0.85; participants = 2256; studies = two; $I^2 = 0\%$; [Analysis 1.23](#)). Both included studies ([Dodd 2014](#); [Vesco 2013](#)) were diet and exercise counselling interventions and were conducted in high-risk populations.

Quality of the evidence

We graded this evidence as moderate quality due to indirectness (may not apply to all types of interventions).

1.24 Postpartum haemorrhage

There was no difference in this outcome between intervention and control groups (average RR 0.94, 95% CI 0.78 to 1.14; participants = 2901; studies = two; $I^2 = 0\%$; [Analysis 1.24](#)).

Quality of the evidence

We graded this evidence as high quality.

2. Diet interventions (low glycaemic load (GL) diet) versus routine care

A maximum of five studies contributed data to this comparison ([Clapp 2002a](#); [Louie 2011](#); [Moses 2014](#); [Rhodes 2010](#); [ROLO 2012](#)).

1. *Excessive GWG*: Low GL dietary interventions significantly reduced the risk of excessive GWG in the intervention group compared with the control group (RR 0.74, 95% CI 0.55 to 0.99; participants = 833; studies = two; $I^2 = 46\%$; [Analysis 2.1](#)). The test for subgroup differences was not significant ($\text{Chi}^2 = 1.30$, $\text{df} = 1$ ($P = 0.25$), $I^2 = 22.9\%$).

2. *Mean GWG*: Due to substantial heterogeneity, we did not pool these data.

3. *Low GWG*: Only one study contributed data ([Louie 2011](#)) and found no statistically significant difference between intervention and control arms ([Analysis 2.3](#)).

4. *Preterm birth*: One study contributed data to two subgroups in this analysis. There was no statistically significant difference between intervention and control groups (average RR 0.33, 95% CI 0.11 to 1.02; participants = 804; studies = two; $I^2 = 0\%$; [Analysis 2.4](#); Test for subgroup differences: $\text{Chi}^2 = 0.21$, $\text{df} = 1$ ($P = 0.65$), $I^2 = 0\%$).

5. *Caesarean delivery*: Two studies contributed data to the high-risk subgroup. There was no statistically significant difference between the intervention and control groups (average RR 0.99, 95% CI 0.33 to 3.01; participants = 133; studies = two; $I^2 = 65\%$; [Analysis 2.5](#)).

6. *Infant birthweight greater than 4000 g*: There was no statistically significant difference between the intervention and control groups (average RR 0.96, 95% CI 0.77 to 1.20; participants = 1472; studies = four; $I^2 = 14\%$; [Analysis 2.6](#); however, the test for subgroup differences suggested that subgroup results may differ in respect to this outcome, with more macrosomia babies born to high-risk women in the intervention group ($\text{Chi}^2 = 2.12$, $\text{df} = 1$ ($P = 0.15$), $I^2 = 52.9\%$).

7. *Pre-eclampsia*: no data available.

We graded the evidence relating to excessive GWG as moderate quality, and for the other outcomes analysed as low quality due to heterogeneity or imprecision and sparse data, therefore it is likely that further research may change these effect estimates.

3. Diet and exercise counselling versus routine care

A maximum of 13 studies contributed data to these meta-analyses. To avoid duplication of data from [Althuisen 2013](#) we did not combine subgroup data.

1. *Excessive GWG*: Interventions reduced the incidence of excessive GWG in low-risk participants (average RR 0.72, 95% CI 0.55 to 0.95; participants = 247; studies = 2; $I^2 = 0\%$) and there was a trend towards a reduction in excessive GWG in the high-risk subgroup (RR 0.85, 95% CI 0.71 to 1.02; participants = 2725; studies = nine; $I^2 = 69\%$; [Analysis 3.1](#); Test for subgroup differences: $\text{Chi}^2 = 3.51$, $\text{df} = 2$ ($P = 0.17$), $I^2 = 43.0\%$). We downgraded this evidence to moderate due to heterogeneity.

2. *Mean GWG*: Mean GWG in kg was reduced with the intervention for the mixed-risk subgroup (MD -1.80, 95% CI -3.36 to -0.24; participants = 444; studies = three; $I^2 = 76\%$) and the high-risk subgroup (MD -0.71, 95% CI -1.34 to -0.08; participants = 2741; studies = 11; $I^2 = 57\%$) but heterogeneity was high ([Analysis 3.2](#)). In the latter, this could be explained by the timing of the measurements, and when two studies that measured weight gain at less than 34 weeks were excluded, data were homogeneous and favoured no clear difference between the intervention and control groups (MD -0.15, 95% CI -0.44 to 0.15; participants = 2424; studies = nine; $I^2 = 0\%$; Test for

subgroup differences suggested a difference in effect between subgroups: $\text{Chi}^2 = 5.44$, $\text{df} = 2$ ($P = 0.07$), $I^2 = 63.2\%$).

3. *Low GWG*: There was no significant difference in low GWG on average overall (RR 1.23, 95% CI 0.89 to 1.72; participants = 2552; studies = five; $I^2 = 49\%$; [Analysis 3.3](#); Test for subgroup differences: $\text{Chi}^2 = 0.07$, $\text{df} = 1$ ($P = 0.79$), $I^2 = 0\%$) or for subgroups; however the overall trend favoured the control group.

4. *Preterm birth*: There was no significant difference in preterm birth on average overall (RR 0.94, 95% CI 0.57 to 1.55; participants = 3170; studies = seven; $I^2 = 52\%$; [Analysis 3.4](#)) or for subgroups; Test for subgroup differences: $\text{Chi}^2 = 0.32$, $\text{df} = 1$ ($P = 0.57$), $I^2 = 0\%$). We downgraded this evidence to low due to imprecision and heterogeneity.

5. *Pre-eclampsia*: There was no significant difference in pre-eclampsia on average between intervention and control groups for the high-risk population (average RR 1.06, 95% CI 0.79 to 1.43; participants = 2896; studies = seven; $I^2 = 0\%$; [Analysis 3.5](#)). Only one study contributed events to the low-risk subgroup.

6. *Caesarean delivery*: Interventions reduced the incidence of caesarean section on average (RR 0.89, 95% CI 0.80 to 1.00; participants = 3406; studies = nine; $I^2 = 3\%$; [Analysis 3.6](#); $P = 0.05$; borderline statistical significance). This trend was consistent across risk subgroups; Test for subgroup differences: $\text{Chi}^2 = 1.53$, $\text{df} = 2$ ($P = 0.46$), $I^2 = 0\%$.

7. *Infant birthweight greater than 4000 g*: There was no statistically significant difference in macrosomia on average between intervention and control groups overall (RR 0.92, 95% CI 0.77 to 1.11; participants = 3705; studies = 10; $I^2 = 7\%$; [Analysis 3.7](#)). or for the low-risk or mixed-risk subgroups. However, in the high-risk subgroup an effect in favour of a reduction in macrosomia was of borderline statistical significance (average RR 0.85, 95% CI 0.73 to 1.00; participants = 3252; studies = nine; $I^2 = 0\%$; $P = 0.05$) and the test for subgroup differences was statistically significant ($\text{Chi}^2 = 3.86$, $\text{df} = 1$ ($P = 0.05$), $I^2 = 74.1\%$).

We graded the evidence for diet and exercise counselling interventions as moderate quality, except for the outcome preterm birth which we graded as low quality.

4. Exercise interventions versus routine care

A maximum of 13 studies contributed data to these analyses. Three studies ([Kong 2014](#); [Renault 2014](#); [Ronnberg 2014](#)) involved unsupervised (as opposed to supervised) exercise interventions and we performed sensitivity analyses to determine whether including unsupervised exercise intervention studies had an impact on the results. To avoid duplication of data, where individual studies contributed data to both risk subgroups ([Ronnberg 2014](#); [Ruiz 2013](#)), we did not combine subgroup data.

1. *Excessive GWG*: Exercise interventions significantly reduced this outcome consistently across risk subgroups with point

estimates for low, mixed and high risk subgroups of 0.69, 0.77, and 0.84 respectively ([Analysis 4.1](#)). Test for subgroup differences were not significant: $\text{Chi}^2 = 1.36$, $\text{df} = 2$ ($P = 0.51$), $I^2 = 0\%$.

2. *Mean GWG*: When one study at a high risk of bias ([Price 2012](#)) was excluded from the mixed-risk subgroup, the intervention was associated with a statistically significant reduction in mean weight gain in kg compared with the control in the mixed-risk subgroup (MD -1.35, 95% CI -1.80 to -0.89; participants = 1134; studies = three; $I^2 = 0\%$), and low risk subgroup (one study only), but not the high-risk subgroup (MD -0.32, 95% CI -1.15 to 0.50; participants = 476; studies = four; $I^2 = 0\%$; [Analysis 4.2](#)). Test for subgroup differences suggested a difference in effect between subgroups: $\text{Chi}^2 = 5.78$, $\text{df} = 2$ ($P = 0.06$), $I^2 = 65.4\%$.

3. *Low GWG*: There was an increase in low GWG of borderline statistical significance between intervention and control groups for the mixed risk subgroup (average RR 1.20, 95% CI 1.00 to 1.43; participants = 1336; studies = two; $I^2 = 0\%$; $P = 0.05$) and low risk subgroup (one study only) but not the high-risk subgroup (average RR 1.03, 95% CI 0.66 to 1.60; participants = 504; studies = three; $I^2 = 0\%$; [Analysis 4.3](#)). Test for subgroup differences were not significant: $\text{Chi}^2 = 0.98$, $\text{df} = 2$ ($P = 0.61$), $I^2 = 0\%$.

4. *Preterm birth*: There was no statistically significant difference in preterm birth on average between intervention and control groups for the low risk (one study only), mixed risk (average RR 1.92, 95% CI 0.75 to 4.93; participants = 1129; studies = three; $I^2 = 0\%$) or the high-risk subgroup (average RR 1.34, 95% CI 0.51 to 3.55; participants = 504; studies = three; $I^2 = 0\%$; [Analysis 4.4](#)); however the trend consistently favoured the control group. The test for subgroup differences was not significant: $\text{Chi}^2 = 0.27$, $\text{df} = 1$ ($P = 0.60$), $I^2 = 0\%$.

5. *Pre-eclampsia*: There was no statistically significant difference in pre-eclampsia overall between intervention and control groups (average RR 0.99, 95% CI 0.58 to 1.66; participants = 1253; studies = four; $I^2 = 0\%$; [Analysis 4.5](#)) and subgroup findings were similar: Test for subgroup differences: $\text{Chi}^2 = 0.51$, $\text{df} = 1$ ($P = 0.48$), $I^2 = 0\%$.

6. *Caesarean delivery*: There was no statistically significant difference in caesarean delivery between intervention and control groups for low risk (one study only), mixed risk (average RR 0.96, 95% CI 0.76 to 1.22; participants = 2263; studies = six; $I^2 = 24\%$) or the high-risk subgroup (average RR 0.98, 95% CI 0.81 to 1.20; participants = 645; studies = five; $I^2 = 0\%$; [Analysis 4.6](#)); . Test for subgroup differences: $\text{Chi}^2 = 0.37$, $\text{df} = 2$ ($P = 0.83$), $I^2 = 0\%$.

7. *Infant birthweight greater than 4000 g*: There was no statistically significant difference in macrosomia between intervention and control groups for the low-risk (one study only), mixed-risk (average RR 0.81, 95% CI 0.64 to 1.02; participants = 2445; studies = seven; $I^2 = 0\%$) or the high-risk subgroups (RR 0.65, 95% CI 0.22 to 1.91; participants = 504; studies = three; I^2

= 74%; [Analysis 4.7](#) Test for subgroup differences: $\text{Chi}^2 = 0.14$, $\text{df} = 1$ ($P = 0.71$), $I^2 = 0\%$. However, the trend across subgroups consistently favoured the intervention, and the effect for the mixed-risk subgroup was of borderline statistical significance ($P = 0.07$). Furthermore, when three studies with risk of bias concerns were excluded ([Cordero 2014](#); [Murtezani 2014](#); [Stafne 2012](#)), the RR for the mixed-risk population clearly favoured the intervention group (average RR 0.56, 95% CI 0.36 to 0.88; participants = 1274; studies = eight; $I^2 = 0\%$).

As the number of studies included in most analyses were few, we did not assess funnel plots. Including studies of unsupervised exercise did not have a significant impact on the results. We graded this evidence as moderate quality overall, except for the evidence on preterm birth (low quality) which was very imprecise and potentially subject to a serious risk of attrition and/or reporting bias.

5. Diet and supervised exercise interventions versus routine care

A maximum of five studies contributed data to these analyses; two studies contributed data to each of the mixed- and high-risk subgroups, one study ([Hui 2014](#)) reported results separately for both subgroups, therefore we were able to pool these data.

1. *Excessive GWG*: Combined exercise and diet interventions significantly reduced excessive weight gain (average RR 0.75, 95% CI 0.61 to 0.92; participants = 689; studies = five; $I^2 = 18\%$, [Analysis 5.1](#); When one study at high risk of bias was excluded ([Ruchat 2012](#)), the test for subgroup differences suggested that there might be a difference in effect according to risk, with a smaller effect in the high-risk subgroup: Test for subgroup differences: $\text{Chi}^2 = 4.54$, $\text{df} = 2$ ($P = 0.10$), $I^2 = 55.9\%$.

2. *Mean GWG*: The interventions reduced mean GWG compared with controls (average MD -1.31, 95% CI -3.00 to 0.37; participants = 348; studies = three; $I^2 = 43\%$; borderline significance, [Analysis 5.2](#)). However, the test for subgroup differences suggested that there might be a difference in effect according to risk, with a smaller effect in the high-risk subgroup: Test for subgroup differences: $\text{Chi}^2 = 4.90$, $\text{df} = 2$ ($P = 0.09$), $I^2 = 59.2\%$.

3. *Low GWG*: Only one study showing no difference contributed data to this outcome ([Analysis 5.3](#)).

4. *Preterm birth*: No data available

5. *Pre-eclampsia*: Only one study showing no difference contributed data to this outcome ([Analysis 5.4](#)).

6. *Caesarean delivery*: There was no statistically significant difference in the risk of caesarean delivery between intervention and control groups (average RR 1.00, 95% CI 0.69 to 1.45; participants = 607; studies = three; $I^2 = 0\%$; [Analysis 5.5](#); Test for subgroup differences: $\text{Chi}^2 = 0.29$, $\text{df} = 1$ ($P = 0.59$), $I^2 = 0\%$).

7. *Infant birthweight greater than 4000 g*: There was no statistically significant difference between groups for this

outcome (RR 1.02, 95% CI 0.71 to 1.46; participants = 398; studies = three; $I^2 = 0\%$; [Analysis 5.6](#); Test for subgroup differences: $\text{Chi}^2 = 0.33$, $\text{df} = 1$ ($P = 0.56$), $I^2 = 0\%$).

We graded this evidence from analyses as low-to-moderate quality due to imprecision (sparse data) and some inconsistencies.

6. Diet counselling only versus routine care

A maximum of seven heterogeneous studies contributed data to these analyses ([Di Carlo 2014](#); [Jeffries 2009](#); [Laitinen 2009](#); [Quinlivan 2011](#); [Rae 2000](#); [Thornton 2009](#); [Wolff 2008](#)).

1. *Excessive GWG*: We did not combine subgroup data for this analysis as one study contributed data to both subgroups. There was no statistically significant difference between intervention and control arms ([Analysis 6.1](#)). The test for subgroup differences showed that subgroup results were similar: $\text{Chi}^2 = 0.49$, $\text{df} = 1$ ($P = 0.48$), $I^2 = 0\%$.

2. *Mean GWG*: Data for this outcome were very heterogeneous (I^2 greater than 90%) with four out of seven studies finding a difference in mean GWG of greater than 4 kg, with the other three studies finding little difference; therefore, we did not combine these data ([Analysis 6.2](#)).

3. *Low GWG*: Only one study contributed data ([Laitinen 2009](#)), which found that significantly more women in the intervention arm had low GWG compared with the control arm ([Analysis 6.3](#)).

4. *Preterm birth*: There was no statistically significant difference in the risk of preterm birth between intervention and control groups (average RR 0.67, 95% CI 0.26 to 1.73; participants = 591; studies = three; $I^2 = 0\%$, [Analysis 6.4](#)); Test for subgroup differences: $\text{Chi}^2 = 0.00$, $\text{df} = 1$ ($P = 0.99$), $I^2 = 0\%$.

5. *Pre-eclampsia*: There was no statistically significant difference in the risk of pre-eclampsia between intervention and control groups (RR 0.90, 95% CI 0.54 to 1.48; participants = 634; studies = four; $I^2 = 0\%$; [Analysis 6.5](#); Test for subgroup differences: $\text{Chi}^2 = 2.05$, $\text{df} = 1$ ($P = 0.15$), $I^2 = 51.2\%$).

6. *Caesarean section*: There was no statistically significant difference in the risk of caesarean delivery between intervention and control groups (average RR 1.06, 95% CI 0.93 to 1.21; participants = 754; studies = five $I^2 = 2\%$; [Analysis 6.6](#); Test for subgroup differences: $\text{Chi}^2 = 0.30$, $\text{df} = 1$ ($P = 0.59$), $I^2 = 0\%$).

7. *Infant birthweight greater than 4000 g*: There was no statistically significant difference in the risk of macrosomia between intervention and control groups when data from two studies conducted in high-risk women were pooled (RR 1.81, 95% CI 0.88 to 3.72; participants = 349; studies = two; $I^2 = 0\%$, [Analysis 6.7](#)).

We graded the evidence relating to these interventions as low quality overall due to heterogeneity and risk of bias concerns. As the number of studies included in most analyses were few, we did not assess funnel plots.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Intervention type	Risk group	EGWG	Mean GWG	Low GWG	Preterm birth	Caesarean	Pre-eclampsia	Macrosomia
All interventions (max 36 studies)	Overall	20% reduction (13 to 27%)	Not estimated	14% increase (2% to 27%)	NS	NS	NS	BS (7% reduction, -2% to 14%)
Low GL diet (max 5 studies)	Overall	23% reduction (9% to 33%)	Not estimated	NS	BS in favour of the intervention	NS	NA	NS
	Low	40% reduction (6% to 52%)	NS	NS	NS	NS	NA	NA
	Mixed	21% reduction (1 study)	NS	NA	NS	NS	NA	NS
	High	NS	NS	NS	NS	NS	NA	NS
Diet and exercise counselling (max 13 studies)	Overall	14% reduction (2% to 25%)	Not estimated	NS	NS	BS (13% reduction; -1% to 25%)	NS	NS
	Low	28% reduction (5% to 45%)	NS	NS	NS	NS	NS	NS
	Mixed	NS	1.80 kg reduction (0.24 to 3.36 kg)	NA	NS	BS (34% reduction; -5% to 59%)	NA	NS
	High	NS	0.71 kg reduction (0.08 to 1.34)	NS	NS	BS (11% reduction; -4 to 24%)	NS	15% reduction (0% to 27%)
Exercise (supervised or unsupervised) only (max 10 studies)	Overall	21% reduction (11% to 30%)	Not estimated	BS (19% increase; 0% to 41%)	NS	NS	NS	NS

	Low	BS (31%; -2 to 53%)	1.50 kg reduction (0.92 to 2.08 kg; one study only)	29% increase; 6% to 42%)	BS (one study)	NS	NA	
	Mixed	23% reduction (12% to 34%)	1.35 kg reduction (0.89 to 1.80)	NS	NS	NS	NS	BS* (19% reduction; -2% to 36%)
	High	16% reduction (5% to 27%)	NS	NS	NS	NS	NS	NS
Unsupervised exercise only (max 3 studies)	Overall	17% reduction (3% to 29%)	Not estimated	NS	NS	NS	NS	NS
Supervised exercise only (max 7 studies)	Overall	25% reduction (11% to 37%)	Not estimated	BS (21% increase; -1% to 52%)	NS (trend in favour of control)	NS	NS	BS (19% reduction; -2% to 36%)
Diet and supervised exercise (max 5 studies)	Overall	29% reduction (15% to 41%)	NS	NS	NA	NS	NS	NS
	Low	NS	3.33 kg reduction (1.21 to 5.45; one study only)	NA	NA	Not estimable	NA	NA
	Mixed	36% reduction (16% to 52%)	1.69 kg reduction (0.11 to 3.48)	NS	NA	NS	NA	NS
	High	NS	NS	NA	NA	NS	NA	NS
Diet counselling/ other (max 7 studies)	Overall	NS	Not estimated	NS	NS	NS	NS	NS
	Mixed	NS	NA	NA	NS	NS	NS	NA
	High	NS	NA	NA	NS	NS	NS	NS

Finding are presented with reference to the intervention group

* Sensitivity analysis suggested that there may be a statistically significant difference in favour of the intervention for the mixed-risk subgroup.

Abbreviations: NA = not available; NS = not statistically significant ($P \geq 0.05$); BS = borderline significance

DISCUSSION

Summary of main results

This updated review included 65 randomised controlled trials (RCTs) in total with 49 RCTs involving at least 11,444 participants contributing data to quantitative synthesis. Twenty RCTs were considered to be at moderate-to-high risk of bias. Where these studies contributed data (14 studies), we performed sensitivity analysis to determine how including these data impacted on the results. Diet interventions most commonly involved a low GL, diabetic, calorie-controlled or low fat diet; exercise interventions were most commonly of moderate intensity involving walking, dance, or aerobic classes. Most included studies were conducted in developed countries. Overall findings are summarised in [Summary of findings for the main comparison](#). Diet or exercise, or both, interventions reduced the risk of excessive gestational weight gain (GWG) by an average of 20% (95% CI, 13 to 27%) overall. Data were moderately heterogeneous; however this overall effect was robust to sensitivity analysis and consistent across the different types of interventions, therefore we graded this evidence as high quality. The greatest effect on excessive GWG was noted for combined diet plus supervised exercise interventions.

Data for mean GWG were too heterogeneous to pool and were inconsistent between, and frequently within, the different types of intervention groups, therefore, we did not pool these data. However, for subgroup analyses according to the risk of weight-related complications, we pooled data if heterogeneity was mild or moderate, and downgraded the evidence accordingly. Limited evidence from diet and exercise counselling interventions, exercise only interventions, and diet and supervised exercise interventions suggested that there might be a difference in effect on mean weight gain according to risk, with a smaller effect in the high-risk subgroups (*low quality evidence*).

Women receiving diet or exercise, or both interventions were more likely to experience low GWG than controls (average risk ratio (RR) 1.14, 95% confidence interval (CI) 1.02 to 1.27; participants = 4422; studies = 11; $I^2 = 3$; *moderate-quality evidence*). We found no difference between intervention and control groups with regard to pre-eclampsia (RR 0.95, 95% CI 0.77 to 1.16; participants = 5330; studies = 15; $I^2 = 0$; *high-quality evidence*); however, maternal hypertension (not a pre-specified outcome) was reduced in the intervention group compared with the control group overall (average RR 0.70, 95% CI 0.51 to 0.96; participants = 5162; studies = 11; $I^2 = 43$; *low-quality evidence*).

There was no clear difference between groups with regard to caesarean delivery overall (RR 0.95, 95% CI 0.88 to 1.03; participants = 7534; studies = 28; $I^2 = 9$; *high-quality evidence*); although the effect estimate suggested a small difference (5%) in favour of the interventions. In addition, for combined diet and exercise counselling interventions there was a 13% (-1% to 25%) reduction in this outcome (borderline statistical significance).

We found no difference between groups with regard to preterm birth overall (average RR 0.91, 95% CI 0.68 to 1.22; participants = 5923; studies = 16; $I^2 = 16$; *moderate-quality evidence*); however limited evidence suggested that these effect estimates may differ according to the types of interventions, with a trend towards an increased risk for exercise-only interventions.

We found no clear difference between intervention and control groups with regard to infant macrosomia overall (average RR 0.93, 95% CI 0.86 to 1.02; participants = 8598; studies = 27; $I^2 = 0$; *high-quality evidence*), although the effect estimate suggested a small difference (7% reduction) in favour of the intervention group. The largest effect size occurred in the supervised exercise-only intervention group (RR 0.81, 95% CI 0.64 to 1.02; participants = 2445; studies = seven; $I^2 = 0$), which approached statistical significance ($P = 0.07$). Furthermore, in subgroup analysis by risk, high-risk women receiving combined diet and exercise counselling interventions experienced a 15% reduced risk of infant macrosomia (average RR 0.85, 95% CI 0.73 to 1.00; participants = 3252; studies = nine; $I^2 = 0$; $P = 0.05$; *moderate-quality evidence*).

There were no differences in the risk of poor neonatal outcomes including shoulder dystocia, neonatal hypoglycaemia, hyperbilirubinaemia, or birth trauma (all *moderate-quality evidence*) between intervention and control groups; however, infants of high-risk women had a reduced risk of respiratory distress syndrome if their mothers were in the intervention group (RR 0.47, 95% CI 0.26 to 0.85; participants = 2256; studies = two; $I^2 = 0$; *moderate-quality evidence*).

The effect on behaviour modification outcomes, i.e. dietary and physical activity outcomes, in general, favoured the intervention groups; however, these outcomes were at high risk of bias and mainly reflected whether the implementation of the interventions was successful. Low-quality evidence suggested that the beneficial effects of interventions on weight control during pregnancy may be sustained postpartum. For certain outcomes, e.g. childhood weight, we found no data for meta-analysis.

For a brief summary of the effects of the different types of interventions on the main outcomes, see [Summary of findings 2](#).

Overall completeness and applicability of evidence

There is a growing body of evidence to support the use of diet or exercise, or both, interventions to reduce excessive GWG in pregnancy. We found high-quality evidence of other related health benefits for women and newborns, applicable to most pregnant women who are otherwise healthy, irrespective of their prepregnancy weight. Exercise appears to be an important component of weight reduction interventions; however the evidence with regard to the effect of exercise on the risk of preterm birth is of a moderate quality and this outcome should be rigorously evaluated in future studies to enable the establishment of appropriate guidelines. The

evidence is not applicable to women with specific contraindications to exercise in pregnancy or pre-existing medical conditions. Although we included four studies conducted in women with gestational diabetes, data were sparse and it is not clear whether the review findings apply to women with this condition. More research (qualitative and quantitative) to improve outcomes in this high risk group is needed.

Most included studies were carried out in developed countries and it is not clear whether these results are widely applicable to lower income settings with fewer human and financial resources. More research is needed in these less developed settings, where obesity is increasingly a major health issue. Innovative interventions utilising mobile-phone technology (e.g. [Pollak 2014](#)) are of interest and further developments in this area are anticipated.

Quality of the evidence

Using the GRADE approach, we considered the quality of the evidence relating to excessive GWG as high quality. Although moderate heterogeneity was present, we upgraded our assessment of evidence quality from moderate-to-high quality as findings were precise and robust to sensitivity analysis. We graded the evidence with regard to the risk of low GWG as high quality as these estimates were consistent and precise across included studies. We downgraded the evidence with regard to preterm birth (no statistically significant difference) to moderate due to risk of bias concerns from attrition and under-reporting. We graded the quality of the evidence for pre-eclampsia, caesarean delivery and macrosomia as high quality and most other outcomes, as moderate quality. We downgraded some evidence due to heterogeneity. Many factors might have contributed to this heterogeneity including obvious and subtle differences in the types of interventions, types of participants (e.g. BMIs, parity, age), delivery of the intervention (e.g. whether the intervention was incorporated into antenatal visits or delivered separately by a dietician), timing of the measurements (e.g. weight gain assessed at 34 versus 38 weeks), timing of commencement of the intervention (e.g. first, second or third trimester), sample sizes, etc. An in-depth evaluation of individual interventions was beyond the scope of this review; however, our impression was that the more intensely monitored/supervised the intervention, the better the study results.

Potential biases in the review process

We took a number of steps to minimise bias in the review process by including all relevant RCTs, with two review authors independently classifying them, extracting data, and resolving disagreements by discussion with the other authors. Where expected outcome data were missing we made an effort to contact the study investigators, and we included adjusted data from cluster-RCTs where possible. In the previous version of this review we included

two quasi-RCTs ([Bechtel-Blackwell 2002](#); [Moses 2006](#)), which we excluded for this update after deciding to limit the review to RCTs. Due to issues of scope and relevance, we also excluded two early studies of appetite suppressant drugs that had been included in the original review ([Boileau 1968](#); [Silverman 1971](#)).

We considered it clinically meaningful to produce overall estimates of average effects across all studies where possible, organised by the type of intervention, using random effects methods. Interventions were often multifaceted and were quite heterogeneous in approach, for example, in the timing, duration, intensity, content and delivery. Some studies evaluated more than one type of intervention. [Dodd 2014](#), for example, was mainly a diet and exercise counselling intervention study and we included it as such; however, 26% of participants in the intervention arm underwent a supervised walking exercise as part of a nested RCT. Where possible, when heterogeneity existed between studies evaluating apparently similar interventions, which could not be explained by our 'Risk of bias' assessment, we attempted to identify the possible reasons for it. In addition, although we made distinctions between types of diet and exercise interventions according to whether the exercise component was supervised or not, the results were robust on exploratory analyses when all combined diet and exercise intervention data for the main outcomes were pooled.

Two studies compared higher impact interventions with lower impact interventions ([Ruchat 2012](#); [Thornton 2009](#)), and several studies of low GL diets compared the intervention with an alternative (low-fat, moderate/high GL or conventional healthy eating) diet ([Rhodes 2010](#); [Louie 2011](#); [Moses 2009](#); [Moses 2014](#)). For these studies, we pooled the data of the alternative intervention with the control group which, in most other studies, comprised routine care. This may have contributed to heterogeneity in the meta-analyses and might have led to an underestimation of the summary effect of the intervention. [Clapp 2002b](#) compared different exercise intensities at different stages of pregnancy (before versus after 20 weeks' gestation) and found that low-intensity exercise in early pregnancy moving on to higher-intensity exercise after 20 weeks was associated with a lower pregnancy weight gain than either high- followed by low-intensity exercise or moderate-intensity exercise throughout. We did not explore the impact of higher- versus lower-intensity interventions, which may have provided important information for exercise interventions and certain outcomes, such as preterm birth. This was largely due to a sparseness of data and time constraints.

Several studies reported maternal 'hypertension', and not pre-eclampsia, and we extracted and analysed these data. This was not prespecified in the protocol (see [Differences between protocol and review](#)); however, we made every effort to minimise bias in this process, and consider the pooled findings to be of value, albeit low-quality evidence. The effect estimates for hypertension differed from those for pre-eclampsia with a consistent trend towards a reduction in hypertension, but not pre-eclampsia, in intervention arms.

We did not perform meta-analyses according to BMI classification of degree of obesity, although several studies stratified results by BMI (overweight or obese or morbidly obese). In one study that reported these BMI categories separately (Kong 2014), we combined these data for use in our meta-analysis. For studies of high-risk women that reported combined and separate results for overweight and obese categories (Harrison 2013; Petrella 2013; Nascimento 2012), we extracted all data but used the combined data only in our meta-analyses. It is possible that certain types of interventions may be more effective for different high-risk BMI categories and we may try to address this in future versions of this review.

Behaviour modification outcomes may have been subject to potential reviewer bias. Multiple and varied behaviour modification outcomes were reported by the various investigators and we pre-specified only three outcomes (energy intake, fibre intake and a physical activity measure) for inclusion in the review. In addition, numerous different scales and time points were reported by study investigators, a narrative discussion of which is beyond the scope of this review. However, in many respects, behaviour outcome measures are measures of the intervention rather than the effect of the intervention and we consider this outcome to be a poor (indirect) measure of effectiveness of an intervention. In addition, these outcomes were subject to other serious risk of bias concerns, including detection (often self-reported) and attrition bias.

Agreements and disagreements with other studies or reviews

A 2012 UK Health Technology Assessment review (Thangaratinam 2012) included 30 RCTs in a meta-analysis of GWG and reported an overall reduction (± 1 kg) in mean GWG in the intervention group compared with controls. Two other systematic reviews (Ronnberg 2010; Skouteris 2010) that included RCTs and non-randomised studies also reported GWG outcomes in favour of the interventions. Thangaratinam 2012 reported that the largest weight reduction occurred with dietary interventions (a mean reduction of 3.36 kg), which were also effective at reducing gestational hypertension, pre-eclampsia, preterm birth and shoulder dystocia. Due to substantial heterogeneity, we did not pool mean weight gain data and our review does not agree with these findings. Thangaratinam 2012 utilised data from non-randomised studies to provide evidence on adverse effects; however, most of these data were derived from studies on extreme diet and famine and therefore have limited applicability. Randomised controlled trial data on adverse effects remain sparse and we were unable to provide additional evidence in this regard.

We were unable to show a reduced risk of macrosomia overall, as was shown in Thangaratinam 2012, although our findings did not exclude a small reduction in risk. In addition, our findings suggested greater reductions may be achieved for high-risk women who received combined diet and exercise interven-

tions, and women receiving supervised exercise-only interventions. Dodd 2014, the largest study included in this review additionally reported the rate of very high birthweight babies (greater than 4500 g), finding a significant reduction in this outcome in the intervention arm; however, we did not include this outcome.

We found limited evidence that certain interventions were somewhat less effective in reducing GWG in high-risk women compared with the lower-risk group. To our knowledge this has not been previously shown and requires further investigation. Several of our included studies reported gestational diabetes as an outcome and exploratory analysis suggested that the effect of diet and exercise interventions on this outcome might be significant. We did not modify our protocol to include this important outcome as a separate Cochrane review on the topic is in progress (Crane 2013).

AUTHORS' CONCLUSIONS

Implications for practice

High-quality evidence indicates that diet or exercise, or both, during pregnancy can reduce the risk of excessive gestational weight gain (GWG). Other benefits may include a lower risk of caesarean delivery, macrosomia, and neonatal respiratory morbidity, particularly for high-risk women receiving combined diet and exercise interventions. Moderate-intensity exercise appears to be an important part of controlling weight gain in pregnancy, however the evidence on the risk of preterm birth is limited and more research is needed to establish safe guidelines. Most included studies were carried out in developed countries and it is not clear whether these results are widely applicable to lower income settings.

Implications for research

The effectiveness of these interventions in low-income countries and in women with non-Western lifestyles needs further evaluation. In addition, further research is needed, particularly in high-risk women to determine whether other types of diet or adjuvant interventions (e.g. probiotics, metformin), are of value in reducing excessive GWG and improving maternal and infant outcomes. The evidence with regard to the effect of antenatal exercise on the risk of preterm birth is incomplete and this outcome should be carefully monitored and reported by researchers to enable the establishment of appropriate guidelines. Studies of interventions utilising mobile-phone technology are of interest and further developments in this area are anticipated. Research to investigate strategies to implement diet and exercise programs into routine antenatal care in different settings is needed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Althuisen 2013

Methods	RCT, 8 midwifery practices in The Netherlands from February 2005 to May 2006
Participants	246 randomised, 219 analysed. Inclusion criteria: women expecting their first child, able to read and speak Dutch, and in the first 14 weeks of gestation Exclusion criteria: miscarriage, gestation ≥ 15 weeks.
Interventions	Intervention group: counselling (5 x approximately 15 minute sessions on weight, physical activity and diet) (n = 106). Interventions were face-to-face at 18, 22, 30, and 36 weeks' gestation, with a telephone session at 8 weeks postpartum Control group: routine care (no counselling) (n = 113).
Outcomes	Primary outcomes were excessive weight gain, BMI, postpartum weight retention, birth-weight, macrosomia, preterm birth, gestational diabetes
Notes	Age (intervention, control): $29.2 \pm 3.3/30.4 \pm 4$. Enrolment gestational age < 14 weeks. Prepregnancy BMI: $24 \pm 4.2/23.5 \pm 3.8$. Authors concluded that "The lifestyle counselling intervention evaluated in this study did not have an effect on excessive weight gain or postpartum weight retention. Our findings for overweight and obese women need to be confirmed in a larger, randomised trial"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computerised random number generator drew up an allocation schedule pre-stratified for midwifery practices."
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not possible for the intervention.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Research assistants blinded to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	11% of participants (17 in intervention and 10 in control group) dropped out during the course of the study

Althuizen 2013 (Continued)

Selective reporting (reporting bias)	Unclear risk	All expected outcomes reported.
Other bias	Low risk	None noted. Baseline characteristics comparable.

Angel 2011

Methods	RCT conducted at San Francisco General Hospital, USA between 2006 and 2009 (abstract only)
Participants	64 randomised. Inclusion criteria: obese/overweight, ages 18-42 years, from 20 weeks Exclusion criteria: NR.
Interventions	Intervention group: low glycaemic load diet. Control group: low fat diet.
Outcomes	Excessive weight gain, excessive fat gain.
Notes	Age (intervention, control): NR. Enrolment gestational age approx. 20 weeks. Pregnancy BMI: NR. Abstract only with no usable data. "This evidence suggests that dietary patterns are important for achieving weight gain recommendations among overweight and obese pregnant women."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned."
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	14% drop out. Not yet reported in full.
Selective reporting (reporting bias)	Unclear risk	Abstract only with little data.

Other bias	Unclear risk	Abstract only with little data.

Asbee 2009

Methods	RCT, set in resident obstetric clinic in Charlotte, North Carolina, USA
Participants	Inclusion criteria: prenatal care established at 6-16 weeks of gestation, age 18-49 years, all prenatal care received at the Resident Obstetrics Clinic, English-speaking, Spanish-speaking, or both, and singleton pregnancy Exclusion criteria: BMI higher than 40, pre-existing diabetes, untreated thyroid disease, or hypertension requiring medication or other medical conditions that might affect body weight, delivery at institution other than Carolinas Medical Center Main, pregnancy ending in premature delivery (less than 37 weeks), and limited prenatal care (fewer than 4 visits)
Interventions	Intervention group (n = 57) received consistent program of dietary and lifestyle counselling. At the initial visit, participants met with a registered dietician to receive a standardised counselling session, including information on pregnancy-specific dietary and lifestyle choices. The counselling consisted of recommendations for a patient-focused caloric value divided in a 40% CHO, 30% protein, and 30% fat fashion. Participants were instructed to engage in moderate-intensity exercise at least 3 times per week and preferably 5 times per week. They also received information on the appropriate weight gain during pregnancy using the IOM guidelines. Each participant met with the dietician only at the time of enrolment. At each routine obstetrical appointment, the healthcare provider informed the participant whether her weight gain was at the appropriate level. If her weight gain was not within the IOM guidelines, the participant's diet and exercise regimen were reviewed and she was advised on increasing or decreasing her intake and increasing or decreasing exercise Control group (n = 43) received routine prenatal care, including an initial physical examination and history, routine laboratory tests, and routine visits per ACOG standards. The only counselling on diet and exercise during pregnancy was that included in a standard prenatal booklet. The healthcare provider did not counsel the participant regarding any changes in diet or lifestyle
Outcomes	Weight gain, caesarean delivery, pre-eclampsia, shoulder dystocia Total weight gain was defined as weight just before delivery minus prepregnancy weight
Notes	Age (intervention, control): 26.7 ± 6.0, 26.4 ± 5.0. Enrolment gestational age (intervention, control): 13.7 ± 3.6, 13.6 ± 2.2 weeks Prepregnancy BMI: 25.5 ± 6.0, 25.6 ± 5.1 kg/m². BMI category, n (intervention, control): - underweight and normal weight (BMI < 26): 35, 25; - overweight (BMI 26-29.0): 10, 8; - obese (BMI > 29.0): 12, 10.

Risk of bias

Bias	Authors' judgement	Support for judgement

Asbee 2009 (Continued)

Random sequence generation (selection bias)	Low risk	Randomisation was performed using computer-generated random allocation
Allocation concealment (selection bias)	Low risk	Study allocation was concealed in numbered and sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up reported. Trial authors stated that they had carried out an ITT analysis: data were analysed for participants according to their randomly-allocated group; all participants were included in the analysis
Selective reporting (reporting bias)	Low risk	The outcomes reported as in the published protocol.
Other bias	High risk	Demographic data were similar. Age, prepregnancy weight, height and BMI were not different at baseline Women with delivery before 37 weeks were excluded.

Barakat 2011

Methods	RCT, set in Hospital de Fuen-labrada, Madrid, Spain.
Participants	80 women randomised. Inclusion criteria: healthy pregnant women (age, 23-38 years), had uncomplicated, singleton pregnancies Exclusion criteria: any type of absolute obstetric contraindication to aerobic exercise during pregnancy, which included other contraindications that the authors considered to have a relevant influence on maternal perception of health: significant heart disease, restrictive lung disease, incompetent cervix/cerclage, multiple gestation, risk of premature labour, pre-eclampsia/pregnancy-induced hypertension, thrombophlebitis, recent pulmonary embolism (last 5 years), acquired infectious disease, retarded intrauterine development, serious blood disease, and/or absence of prenatal care
Interventions	Intervention group: (40 randomised) moderate physical activity, included a total of 35- to 45-min weekly sessions 3 days each week from the start of the pregnancy (weeks 6-9) to the end of the 3rd trimester (weeks 38-39), an average of 85 training sessions, exercise

	intensity was light-to-moderate. Exercise was supervised by a fitness specialist and was in groups of 10-12 women Control group: (40 randomised) routine care.
Outcomes	Weight gain, caesarean, birthweight < 4000 g, birthweight > 4000 g
Notes	Authors concluded that a moderate physical activity program that is performed over the first, second, and third trimester of pregnancy improves the maternal perception of health status

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned by use of a random number table.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described. It is not clear how lack of blinding would impact on the outcomes measured
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	80 women were randomised and 67 were analysed; 34 in the exercise group, 33 in the control group. Reason of discontinued were similar in both groups
Selective reporting (reporting bias)	Unclear risk	Assessment from published study report.
Other bias	High risk	No between-group differences regarding most potential confounding variables (such as occupational activities, standing, smoking habits, alcohol intake) but parity was not balanced between groups; the exercise group had a higher percentage of nulliparous women (76.5%) than the control group (36.4%)

Bisson 2014

Methods	RCT conducted at Centre Mere Enfant CHU de Quebec, Laval University, Quebec City, Canada
Participants	37 randomised, 4 withdrawals. Numbers in each group not stated Inclusion criteria: obese pregnant women < 15 weeks. Exclusion criteria: NR.
Interventions	Intervention group: 12 week supervised moderate exercise program consisting of 3 weekly 1-hr sessions in a hospital-based setting from 15th to 28th week Control group: routine care.
Outcomes	"perinatal and maternal outcomes."
Notes	Abstract only with no usable data. Exercising women maintained their fitness compared with control women ($P = 0.047$) and "had reduced weekly weight gain (0.3 ± 0.1 kg/wk vs 0.5 ± 0.2 kg/wk for exercise and control, respectively, $p=0.047$." "3 exercising versus 6 control women developed either gestational diabetes or hypertension." "Based on preliminary data, birth weight and gestational age at delivery were comparable between groups (3587 ± 459 g and $39.3/7 \pm 1.1/7$ weeks, vs 3387 ± 409 g and $39.3/7 \pm 1.1/7$ weeks in the exercising and control groups respectively, NS." Authors concluded that "An individualized exercise training effective in maintaining maternal fitness and limiting gestational weight gain in obese, pregnant women does not increase prematurity. However larger gestational weight gain in obese, pregnant women does not increase prematurity. However larger interventional study in this population will determine the potential benefits of maternal exercise during pregnancy on child growth, metabolism and development."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned."
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear due to limited reporting (abstract only) but 4 dropped out. Numbers in each arm was not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Abstract only with sparse data.
Selective reporting (reporting bias)	Unclear risk	Abstract only with sparse data.

Other bias	Unclear risk	Abstract only with sparse data.

Bogaerts 2012

Methods	3-arm RCT conducted in University hospital, Leuven and East Limburg Hospital Belgium
Participants	Inclusion criteria: obese pregnant women. Exclusion criteria: NR.
Interventions	Counselling involving psycho-education (4 sessions) vs a brochure vs control Control group: routine care.
Outcomes	GWG and psychological vulnerability (depression and anxiety)
Notes	Data collected during the first, second and third trimester. They found a significant reduction in GWG in the brochure and prenatal groups compared with controls. No differences in delivery method, birthweight, anxiety or depressed mood noted Authors concluded that: findings justify "the clinical implementation of a psycho-educational program in order to reduce GWG and psychological vulnerability in obese pregnant women"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"women were randomised."
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not provided.
Selective reporting (reporting bias)	Unclear risk	Abstract only with little data.
Other bias	Unclear risk	Abstract only with little data.

Callaway 2010

Methods	RCT, set in a hospital in Brisbane, Australia.	
Participants	50 women randomised. Inclusion criteria: obese pregnant women were recruited at 12 weeks' gestation, aged 18-45, BMI ≥ 30 kg/m ² , pregnancy care at study hospital, willing and able to be randomised to an exercise intervention Exclusion criteria: non-English speaking, contraindication or inability to exercise, medical or obstetric contraindication to exercise including haemodynamically significant heart disease, restrictive lung disease, incompetent cervix (cerclage), multiple gestation, severe anaemia, chronic bronchitis, type 1 diabetes, orthopaedic limitations, poorly controlled seizure disorder, poorly controlled hyperthyroidism, or a heavy smoker	
Interventions	Intervention group: the intervention group received an individualised exercise program with an energy expenditure (EE) goal of 900 kcal/ week. Advice from physiotherapist and diaries for self-monitoring Control group: routine obstetric care.	
Outcomes	Self-report of exercise (behaviour change).	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was by a random number allocation technique conducted by a 3rd party
Allocation concealment (selection bias)	Unclear risk	Not clear but external randomisation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding. The impact of the lack of blinding was not clear. The use of self-monitoring diaries by the intervention group may have introduced recall bias
Incomplete outcome data (attrition bias) All outcomes	High risk	Randomised 50 women, at 36 weeks 36 were followed up (30% attrition)
Selective reporting (reporting bias)	Unclear risk	Assessment from published study report and online supplement
Other bias	Unclear risk	"There were no statistically significant differences between the intervention and control groups in any baseline variable." Differ

		ent monitoring techniques in the 2 groups (diaries in the intervention group) may have led to recall bias

Clapp 2002a

Methods	A prospective randomised design.
Participants	20 healthy women with uncomplicated pregnancy.
Interventions	The participants were enrolled prior to pregnancy and placed on a regular regimen of supervised exercise and began a weight maintaining diet (low glycaemic sources of CHO) . At 8 weeks' gestation, they were randomised to either diet containing low glycaemic CHO sources (n = 10) (aboriginal CHO diet) or high glycaemic CHO sources (n = 10) (cafeteria CHO diet). All continued the same exercise regimen throughout pregnancy
Outcomes	Weight gain. Total weight gain was defined as weight at delivery minus prepregnancy weight
Notes	During pregnancy, all women were allowed to increase caloric intake according to appetite with advancing gestation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unspecified loss to follow-up.
Selective reporting (reporting bias)	High risk	Outcomes not prespecified and appear to be selected.
Other bias	Unclear risk	Poorly reported.

Clapp 2002b

Methods	RCT, set in Case Western Reserve University at metro health medical centre, USA
Participants	Inclusion criteria: 80 healthy, regularly exercising (≥ 3 times/week), non-substance-abusing women were enrolled before pregnancy After conception (which occurred within 4 months in all cases) and ultrasonic confirmation of a viable singleton pregnancy, these women were assigned in week 8 of gestation to the exercise regimens Exclusion criteria: not stated. Number of participants: 75 women enrolled and complete the protocol; 26 in Lo-Hi group, 24 in Mo-Mo group, 25 in Hi-Lo group
Interventions	There were 3 study groups: group 1: low-high exercise (n = 26): exercise 20 mins 5 days a week through to week 20, gradually increasing to 60 mins 5 days a week by week 24 and maintaining that regimen until delivery (Lo-Hi); group 2: moderate-moderate exercise (n = 24): exercise 40 mins 5 days a week from week 8 until delivery (Mod-Mod); group 3: high-low exercise (n = 25): exercise 60 mins 5 days a week through to week 20, gradually decreasing to 20 mins 5 days a week by week 24 and maintaining that regimen until delivery (Hi-Lo)
Outcomes	Weight gain.
Notes	Age 31 ± 1 , 30 ± 1 , 32 ± 1 in Lo-Hi, Mo-Mo, Hi-Lo.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Women were randomly assigned.
Allocation concealment (selection bias)	Unclear risk	Women were randomly assigned by envelope but it was not stated whether envelopes were sequentially numbered, opaque and sealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	High risk	A member of the study team carried out morphometric assessment of placenta and infant at the time of birth
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up 6.25%.
Selective reporting (reporting bias)	Unclear risk	Could not determine.

Clapp 2002b (Continued)

Other bias	Low risk	Baseline data were similar.

Cordero 2014

Methods	Open-label RCT conducted at Hospital Puerta de Hierro, Madrid, Spain
Participants	342 randomised, 257 women analysed. Included pregnant women in Spain at 10-12 weeks according to ultrasound, with no medical or obstetric contraindications to exercise Excluded women with medical or obstetric contraindications.
Interventions	Intervention group (101 women): a supervised exercise program consisting of aerobic and toning exercises for 3 sessions per week. 2 weekly sessions were performed on land (60 min) and 1 session was aquatic based (50 min). Program commenced from 10-14 weeks to the end of the third trimester. Sessions were supervised by a qualified fitness specialist and an obstetrician Control group (156 women): routine care.
Outcomes	GDM (primary outcome, diagnosed by fasting GTT before 30 weeks' gestation, according to medical records). Excessive GWG, gestational age at delivery, mode of delivery, birthweight and length, SGA, macrosomia
Notes	Enrolment age (intervention, control): 33.6 ± 4.1, 32.9 ± 4.5 Enrolment gestational age (intervention, control): NR. Prepregnancy BMI (intervention, control): 22.5 ± 3.2, 23.6 ± 4 NCT01790412.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation and ratio was not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient detail in report.
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition of 21 women (16.4%) in the intervention group and 64 in the control group (29.1%)

Selective reporting (reporting bias)	High risk	Per protocol analysis performed based on adherence to exercise "A minimum of 80% adherence to exercise classes was required for women assigned to the intervention group". Excluded women with poor adherence, and those who developed hypertension or were at risk of preterm labour. Possible side effects of exercise, e.g. preterm labour, were NR
Other bias	High risk	Sample sizes differed substantially (101 and 156 women in intervention and control groups, respectively) For intervention and control groups, respectively, 2.7% vs 4.8% had previous GDM. 17.8% vs 27.6% had sedentary lifestyles before pregnancy. These might have biased GDM and GWG results in favour of the intervention group

De Oliveria Melo 2012

Methods	Open-label 3-arm RCT conducted at Department of Obstetrics, University of Campinas in Brazil with recruitment from May 2008 to Sept 2010
Participants	General population, 187 randomised. Inclusion criteria: healthy pregnant women who were sedentary at admission to the study, gestational age 13 weeks or less confirmed by ultrasonography and with single live fetus Exclusion criteria: excluded if smoked, chronic diseases, a history of premature delivery, fetal abnormalities, placenta previa, a history of vaginal bleeding, placental detachment, and cervical length less than 2.5 cm
Interventions	Intervention group: exercise (initiated at 13 weeks) (n = 62) vs exercise (initiated at 20 weeks) (n = 63) vs control (n = 62). Exercise consisted of walking 3 times a week Control group: routine care.
Outcomes	Uteroplacental blood flow, birthweight, pre-eclampsia, fetal growth restriction, macrosomia (assessed by ultrasound at 38 weeks), LGA and SGA at birth
Notes	Fitness evaluated at 13, 20 and 28 weeks. Age (intervention 1, intervention 2, control): 24 [5.8]/26 [5.3]/24 [5.4] Enrolment gestational age: ≤ 13 weeks. Prepregnancy BMI (intervention 1, intervention 2, control): 24.7 [4.3]/23.4 [3.8]/23.5 [3.5] Authors concluded that "Moderate intensity walking improved the physical fitness level of healthy pregnant previously sedentary women without affecting fetoplacental blood flow or fetal growth"

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation sequence generated in blocks of ten" using Random Allocation software program 1.0."
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes. "Groups were assigned only after the woman agreed to participate."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Investigators involved in monitoring and ...analysis were unaware of the group to which the patient had been assigned."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	16 women declined to participate after randomisation (8.5%). 31 women (19%) were missing follow-up data for the 38 week visit; these missing data were balanced across study arms. Delivery/birth data were available for 161/187 women (86%)
Selective reporting (reporting bias)	Unclear risk	Protocol not seen.
Other bias	Low risk	None noted. Baseline characteristics similar.

Di Carlo 2014

Methods	RCT at antenatal clinic in Italy from January 2010 to January 2011
Participants	General population, 154 randomised, 120 analysed. Inclusion criteria: pregnant at 6-13 weeks' gestation (median 8 weeks). Women were excluded if they had any significant maternal condition Exclusion criteria: any significant maternal condition including essential hypertension, thyroid diseases, gestational diabetes, miscarriages, preterm births, multiple pregnancies with more than 2 fetuses, maternal BMI ≤ 20 and ≥ 40 kg/m ²
Interventions	Intervention group: dietary intervention (personalised diet plan with monthly dietician supervision) (n = 77; 59 in final analysis) Control group: brochure on healthy eating (n = 77; 61 in final analysis)

Outcomes	Weight gain, birthweight.	
Notes	Age (intervention, control): 31.3 [4.7]/28.2 [5.3] (P = 0.002) Enrolment gestational age: 8-13 weeks (median 8 weeks). Prepregnancy BMI: 26.5 [6.3]/25 [4.2] (P = 0.3). Authors concluded that ”This study suggests that a personalised nutritional intervention, in which the dietician plays an active role within the obstetric team, may represent a successful approach to limiting weight gain in pregnant women“	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	”Randomly allocated“ in 1:1 ratio.
Allocation concealment (selection bias)	Low risk	” ...attached a sequentially numbered, opaque sealed and stapled envelope containing the allocation treatment to the patient clinical record.“
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not blinded due to nature of intervention.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	”The allocation sequence was concealed from the researchers.“
Incomplete outcome data (attrition bias) All outcomes	High risk	22% of participants were excluded due to miscarriages (9 vs 8 in diet and control groups respectively), loss to follow-up (6 vs 7) and preterm births (3 vs 1). ”Analysis was performed per protocol“ but protocol deviations and individual denominators were NR
Selective reporting (reporting bias)	High risk	Per protocol data reported with individual denominators missing from most results. Results not adjusted for baseline difference in maternal age (older in the intervention group)
Other bias	High risk	Baseline difference in age of women (average of 3 years older in intervention group)

Dodd 2014

Methods	RCT at 3 public maternity hospitals, Adelaide in Australia from June 2008 to December 2011
Participants	High risk (overweight and obese), 2212. Inclusion criteria: women with a singleton pregnancy, between 10 + 0 and 20 + 0 weeks' gestation, and BMI $\geq$ 25 Exclusion criteria: women with type 1 and 2 diabetes were ineligible
Interventions	Intervention group: comprehensive dietary and lifestyle intervention (counselling) (n = 1108) Intervention involved meetings and home visits with advice on dietary, exercise, and behavioural strategies delivered by a dietician and trained research assistants. Exercise advice primarily encouraged women to increase their amount of walking and incidental activity Control group: routine care (n = 1104). A nested RCT was also conducted in which women randomised to the intervention group were further randomised to receive written/verbal education about physical activity (n = 295) or to participate in a supervised walking group of moderate intensity 3 times per week for 40 mins (n = 287)
Outcomes	Primary outcome measures are: incidence of infants born LGA (birthweight $\geq$ 90th centile for gestation and sex). Secondary outcomes included birthweight > 4000 g, hypertension, pre-eclampsia, and gestational diabetes
Notes	Age (intervention, control): 29.3 [5.4]/29.6 [5.3]. Enrolment gestational age (intervention, control): 14 (11.9-17)/14.1 (11.9-17) Recruitment BMI: 31 (28.1-35.9)/31.1 (27.7-35.6). Authors concluded that "For women who were overweight or obese, the antenatal lifestyle advice used in the study did not reduce the risk of delivering a baby weighing above the 90th centile for gestational age and sex or improve maternal pregnancy and birth outcomes"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The computer generated randomisation schedule used balanced variable blocks in the ratio 1:1". The investigator who prepared the randomisation schedule also was not involved with the recruitment or clinical care
Allocation concealment (selection bias)	Low risk	"Telephoning the central randomisation service."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind participants.

Dodd 2014 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Follow-up done by interviewers not involved with the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 20% missing data for all outcomes.
Selective reporting (reporting bias)	Low risk	All outcomes reported according to protocol.
Other bias	Low risk	None noted. Baseline characteristics comparable.

Ferrara 2011

Methods	RCT at Kaiser Permanente Medical Care Program of Northern California in USA from October 2005 and May 2008	
Participants	High risk (GDM), 197 randomised. Inclusion criteria: women with GDM. Exclusion criteria: age < 18 years; multiple gestation; diagnosis of diabetic retinopathy; high-risk pregnancy (i.e. drug or alcohol abuse, chronic health problems, or pregnancy complications); thyroid diseases diagnosed in the last 30 days; and non-English speaker	
Interventions	Intervention group: lifestyle intervention called DEBI (n = 96). Lifestyle intervention involved 3 in-person sessions and up to 15 telephone calls with counselling re diet, physical activity and breastfeeding up to 12 months postpartum. The intervention was delivered by 2 dietitians. Participants were encouraged to engage in moderate intensity physical activity for 150 mins per week and received written materials about food size, foods with low GI or low fat, and how to read food labels were discussed Control group: routine care (n = 101).	
Outcomes	Meeting a set postpartum weight goal, weight gain, birthweight and breastfeeding	
Notes	Data collected at baseline (GDM diagnosis) and at 6 weeks, 7 months and 12 months Enrolment gestational age (intervention, control): 31 [5.6]/31 [6.1] Authors concluded that: "This study suggests that a lifestyle intervention that starts during pregnancy and continues postpartum is feasible and may prevent pregnancy weight retention and help overweight women lose weight. Strategies to help postpartum women overcome barriers to increasing physical activity are needed"	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computer randomisation program was used to ensure that the conditions remained balanced with regards to the following char-

Ferrara 2011 (Continued)

		acteristics: age(< 30 and ≥ 30 years), parity (≤ 1 and < 1), pregravid BMI (< 27.0 and ≥ 27 kg/m ²).“
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not blinded due to nature of intervention.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	”data were collected by research assistants who were unaware of the condition assignment.“
Incomplete outcome data (attrition bias) All outcomes	High risk	20% attrition at 7 and 12 months follow-up with great loss to follow-up in the intervention groups. This could bias results in the direction of the intervention if the heavier women chose to drop out
Selective reporting (reporting bias)	Unclear risk	Protocol not seen. GWG was NR.
Other bias	Low risk	Baseline characteristics comparable.

Guelinckx 2010

Methods	RCT, set in the prenatal clinic, University Hospital of Leuven, Belgium
Participants	Inclusion criteria: obese (BMI > 29.0 according to IOM criteria), white women consecutively attending the prenatal clinic before 15 week of gestation Exclusion criteria: pre-existing diabetes or developing GDM, multiple pregnancy, recruitment after 15 weeks of gestational age, premature labour (delivery before 37 week of gestation), primary need for nutritional advice in case of a metabolic disorder, kidney problems, Crohn's disease, allergic conditions, and inadequate knowledge of the Dutch language
Interventions	2 intervention groups: the passive group (n = 37): received a brochure during the 1st prenatal consultation. This brochure was specifically designed for the study and provided advice on nutrition and on physical activity and tips to limit pregnancy-related weight gain. The active group (n = 42): received the same brochure and women were actively counselled by a trained nutritionist in 3 group sessions. A maximum of 5 women were brought together in these 1-hour sessions, which were scheduled at 15, 20, and 32 weeks of pregnancy. The sessions provided participants with recommendations on a balanced, healthy diet, based on the Oficial National Dietary Recommendations (9%-11% of the energy should come from proteins, 30%-35% from fat, and 50%-55% from CHOs) Control group (n = 43): received routine prenatal care. (Energy intake was not restricted in any group.)

Outcomes	Excessive weight gain (weight gain more than the upper limit recommendation for overweight women; > 11.2 kg) Gestational weight gain. Obstetrical and neonatal outcome: pre-eclampsia, induction of labour, caesarean section, birthweight > 4000 g Average energy intake. Weight gain was defined as weight at birth minus prepregnancy weight Total physical activity score at 3rd trimester. For analysis 3.10 and 4.10 a physical activity score was calculated by using a questionnaire including a total 16 questions classified into 3 domains: work, sports, and non-sports leisure-time activities, scored on a 5-point scale, ranging from “never”, “seldom”, “sometimes”, “very often”, to “always”. A total score for physical activity from a minimum of 3 to a maximum of 15 was obtained. A higher score indicated more activity
Notes	Age 29.4 ± 4.4, 28.7 ± 4.0, 28.0 ± 3.6 years for control group, passive group, active group Enrolment gestational age: 10.2 ± 2.4, 10.2 ± 2.6, 9.3 ± 2.8 weeks for control group, passive group, active group Prepregnancy BMI: 33.5 ± 3.9, 33.4 ± 3.07, 34.1 ± 4.5 kg/m² for control group, passive group, active group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided.
Allocation concealment (selection bias)	Low risk	Patients were randomly assigned by using block randomisation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up 9.7%. Reasons for excluding the participants from each group were similar
Selective reporting (reporting bias)	Unclear risk	Could not determine.
Other bias	Low risk	Baseline characteristics of participants were similar between intervention and control groups

Haakstad 2011

Methods	Parallel-arm RCT at Norwegian School of Sport Sciences in Norway from September 2007-March 2008	
Participants	General population, 105. Inclusion criteria: ability to speak Norwegian; nulliparous, sedentary women whose exercise levels did not include participation in a structured exercise program including brisk walks for the past 6 months were eligible for the trial, and must be in their first 24 weeks of pregnancy Exclusion criteria: history of more than 2 miscarriages, severe heart disease (including symptoms of angina, myocardial infarction or arrhythmias), persistent bleeding after 12 weeks of gestation, multiple pregnancy, poorly controlled thyroid disease, pregnancy-induced hypertension or pre-eclampsia, diabetes or gestational diabetes, and other diseases that could easily interfere with participation	
Interventions	Intervention group: exercise (60 min supervised aerobic dance at least twice a week for a minimum of 12 weeks) (n = 52). Women in the exercise group were advised to have moderate, self-imposed physical activity on the remaining weekdays Control group: routine care (n = 53).	
Outcomes	Infant birthweight, excessive weight gain, postpartum weight retention. Maternal weight gain and the proportion of women with excessive weight gain according to IOM recommendations (used self-reported pre-pregnancy weight as baseline)	
Notes	Participants were assessed 3 times: first visit (12-24 weeks), second visit (36-38 weeks) and last visit (6-12 weeks postpartum). Adherence was a problem - 31 (60%) women attended less than 80% of the exercise sessions and 4 women never showed up. Investigators performed subgroup analysis of participants who attended more than 24 sessions and the difference was significant in this subgroup of 21 women vs 53 controls (GWG 11.0 vs 13.8; P = 0.01). No women in this group had excessive weight gain (P = 0.006) Age (intervention, control): 31.2 [3.7]/30.3 [4.4]. Enrolment gestational age (intervention, control): 17.3 [4.1]/18 [4.3] Prepregnancy BMI: 23.8 [3.8]/23.9 [4.7]. Authors concluded that "Regular participation in aerobic dance exercise can contribute to significantly reduced weight gain in pregnancy." However, "not associated with a reduction in birth weight"	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used "a simple (not block) computerised randomisation programme"
Allocation concealment (selection bias)	Low risk	"An independent person...assigned the participants to either an exercise group or a control group."

Haakstad 2011 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participant blinding not possible but principal investigator was blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Assessor blinded". The principal investigator was "blinded to group allocation when assessing the outcome measures"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out rates of 19% and 21% in exercise and control arms, respectively. Drop-outs were due to pain, hypertension, preterm birth and other reasons and were similar between the study arms
Selective reporting (reporting bias)	Unclear risk	Could not determine.
Other bias	Unclear risk	Denominators in report tables were the total exercise and control group N, despite stating drop-outs in each group of 10 and 11 women, respectively

Harrison 2013

Methods	RCT at 3 large tertiary hospitals in Victoria, Australia.
Participants	High risk, 228 randomised; 203 analysed. Inclusion criteria: women 12-15 weeks of gestation, overweight (BMI ≥ 25 or ≥ 23 kg/m ²) if high risk ethnicity (Polyasian, Asian, African populations) or obese (BMI ≥ 30 kg/m ²), and at the increased risk for developing GDM identified by validated risk prediction tool Exclusion criteria: exclusion criteria included multiple pregnancies, diagnosed type 1 or 2 diabetes, a BMI ≥ 45 kg/m ² , a pre-existing chronic medical condition, and non-English speaking women
Interventions	Intervention group: lifestyle counselling intervention program (individual 4 sessions based on Social Cognitive Theory provided by a health coach) (n = 121) Intervention provided dietary advice, simple healthy eating, and "physical activity messages" and weight gain self-monitoring. Also included "regular self-weighing as a key behavioural strategy" Control group: routine care (n = 107).
Outcomes	The primary outcome was GWG with secondary outcomes including GDM screening
Notes	Outcomes were assessed at 12-15 and 26-28 weeks' gestation. Postpartum outcomes NR in primary report Age (intervention, control): 32.4 [4.6]/31.7 [4.5]. Enrolment gestational age (overall): 14 [0.8]. Recruitment BMI: 30.4 [5.6]/30.3 [5.9].

	Authors concluded that "Results indicate that a low-intensity lifestyle intervention, integrated with antenatal care, optimizes healthy GWG and attenuates physical activity decline in early pregnancy Efficacy in limiting weight gain was greatest in overweight women and in high-risk ethnically diverse women"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomly assigned ...through computer-generated randomised sequencing."
Allocation concealment (selection bias)	Unclear risk	"Sealed opaque envelopes."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Care providers....were blinded to group allocation."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Participants wore a blinded pedometer" and "investigators and outcome data analysts were blinded to group allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up was similar in the 2 groups and < 20% for primary outcomes. Pedometer (PA) outcomes showed high loss to follow-up; therefore we did not use these data
Selective reporting (reporting bias)	Unclear risk	Could not determine.
Other bias	Unclear risk	Follow-up weight gain data were collected at 28 weeks (much earlier than other included studies)

Hawkins 2014

Methods	Parallel arm pilot RCT. Conducted at medical centres in Western Massachusetts, USA. Recruitment from April 2010 to Aug 2011
Participants	68 high-risk (overweight and obese) pregnant women randomised Overweight and obese pregnant Hispanic women (pre-pregnancy BMI > 25 kg/m ²) aged 18-40 years, with a gestational age of < 18 weeks, and who self-reported participating in < 30 mins of moderate-intensity activity per week Excluded if history of Type 2 diabetes, hypertension, heart disease or chronic renal disease; current medications that adversely influence glucose tolerance; contraindications to participating in moderate-intensity physical activity or a low-fat/high-fibre diet; self-reported participation in > 30 min of moderate-intensity exercise on > 3 days/week or

	> 20 min of vigorous-intensity exercise on > 1 day/week; or 6) multiple gestation (e.g. twins)
Interventions	A lifestyle intervention (n = 33), consisting of a culturally and linguistically modified, motivationally targeted, individually tailored 6-month prenatal programme. Educators encouraged women to achieve guidelines for physical activity, decrease saturated fat and increase dietary fibre. The intervention consisted of 6 monthly in-person behavioural counselling sessions and 5 telephone booster sessions with follow-up to 6 weeks postpartum. Women were encourage to achieve ≥ 30 min of moderate-intensity activity on most days of the week through walking and developing a more active lifestyle Controls had routine care (n = 35).
Outcomes	GWG, infant birthweight and biomarkers of insulin resistance
Notes	Mean recruitment age and BMI not given; these baseline variables were stratified and reported as categorical variables. Mean recruitment age was 14.9 weeks overall. Group characteristics were similar Exercise outcomes were reported for 24-28 weeks' gestation and at 6 weeks' postpartum "Findings suggest that a motivationally matched lifestyle intervention is feasible and may help attenuate pregnancy-related decreases in vigorous physical activity in a population of overweight and obese Hispanic women." NCT01141582

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomisation was stratified by age and prepregnancy BMI with a block size of four."
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not clearly described.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors blinded to the assigned intervention group.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition.
Selective reporting (reporting bias)	Unclear risk	Birth outcomes other than birthweight, and maternal weight at 6 weeks postpartum, were NR
Other bias	Low risk	Baseline characteristics similar. Analysis by ITT.

Huang 2011

Methods	RCT; 3 groups intervention design; 2 experimental groups (from pregnancy to 6 months postpartum (EP) and from birth to 6 months postpartum (EPP). The group receiving the intervention in the postnatal period only is not included in our analysis) and 1 comparison group	
Participants	From January to June 2006, pregnant women were recruited from the obstetric clinics of a hospital in Taiwan (160 women randomised) Inclusion criteria: 16 gestational weeks, age 18 years or older, no cognitive impairment or psychiatric illness, ability to speak and read Chinese, not participating in another study, and intention to give birth at the study site	
Interventions	Intervention group: (80 participants). The educational intervention began at 16 gestational weeks (baseline) and to 6 months postpartum. The intervention was delivered at regularly scheduled clinic visits by nurses with training in nutrition and physical tness. The nurse discussed with each participant how to design an individualised diet and physical activity plan. The intervention consisted of 6 1-to-1 counselling sessions: 1 primary session (about 30-40 mins) at the 16-week gestation visit, and 5, 1-to-1 booster sessions (at 28 gestational weeks, 36-38 gestational weeks, before hospital discharge after a 3-7-day stay, 6 weeks' postpartum and 3 months postpartum). After each clinic visit, women in the experimental groups were sent a personalised graph of their weight changes. At the 1st session, the experimental groups also received a researcher-prepared brochure that provided detailed information on weight management goals during pregnancy and postpartum Control group: (80 participants) routine care, provided once each trimester, which included health education on nutrition and exercise during pregnancy	
Outcomes	GWG, weight retention at 6 months postpartum, health-promoting behaviour; physical activity For analysis 1.9.1 physical activity measurement was a part of the health-promoting lifestyle profile composed of 50-item scale uses a 4-point response format (range = 50-200) to measure the frequency of engaging in activities related to self-actualisation, nutrition, physical activity,interpersonal support, health responsibility and stress management	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using a table of random numbers.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.

Huang 2011 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	The research assistant collecting outcome data was reported to be blind to the group assignments
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	80 women in each group were randomised, 61 and 64 of intervention and control group were analysed (78% followed up)
Selective reporting (reporting bias)	Unclear risk	Assessment from published study report.
Other bias	Low risk	No notable baseline differences were found between groups.

Hui 2006

Methods	RCT, set in a community nurse-managed centre and the Manitoba Clinic, both in urban Winnipeg, Manitoba, Canada	
Participants	Inclusion criteria: women < 26 weeks pregnant with no pre-existing diabetes were recruited on a voluntary basis Exclusion criteria: pregnant women who had medical obstetric, skeletal or muscular disorders that could contraindicate physical exercise during pregnancy	
Interventions	Intervention (n = 24): additional intervention: lifestyle intervention including exercise intervention and dietary intervention Exercise intervention: participants were instructed in group-session exercises and in home-based exercise. Weekly group session included floor aerobics, stretching and strength exercises, 3-5 times/week for 30-45 mins per session, video provided to participants to assist with home-based exercise Nutrition intervention: computer-assisted food choice map interview, dieticians provided a personalised plan for participants Control (n = 21): standard care group received an information package on diet and physical activity for a healthy pregnancy	
Outcomes	Excessive weight gain, weight gain, caesarean section, infant birthweight > 4000 g, and physical activity at end of study Weight gain was defined as weight at birth (from medical chart) minus prepregnancy weight For analysis 1.9.1 physical activity was defined as recreational physical activity which was measured by using the PARmed-X for Pregnancy form based on Health Canada recommendations. Low levels (physical activity = 0) are defined as either no physical activity or activity < 1 to 2 times per week and for < 20 min per session; moderate levels (physical activity = 1) are defined as activity 1 to 2 times per week and for > 20 min per session or > 2 times per week and for < 20 min per session; high level (physical activity = 2) are defined as activity > 2 times per week and for > 20 min per session	

Notes	Age (intervention, control): 26.2 ± 5.7, 26.2 ± 5.4. Prepregnancy BMI (intervention, control): 25 ± 6.3, 23.4 ± 3.9 kg/m² Excessive weight gain was assessed based on prepregnant BMI: • BMI < 20 kg/m², weight gain during pregnancy 12.5 -18 kg; • BMI 20-27 kg/m², upper limit of weight gain 16 kg; • BMI > 27 kg/m², upper limit of weight gain 11.5 kg. (Canadian guidelines for healthy weights) Majority of participants (89%) were from low-income families or low-middle income families	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were enrolled and randomised into additional intervention and standard care groups
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	52 enrolled, 45 completed. Loss = 7/52*100 = 13.5%; 7 pregnant women dropped out due to school or work commitments The participants who dropped out were significantly younger and had lower incomes than those who completed the program (P < 0.01)
Selective reporting (reporting bias)	Unclear risk	Could not determine.
Other bias	Low risk	No significant differences were found in age, prepregnancy BMI, and family income between additional intervention and standard care groups

Hui 2012

Methods	RCT at Tertiary hospital, Winipeg, Canada, from July 2004 to February 2010
Participants	General population, 224 randomised, 190 completed the study (88 controls and 102 interventions) Inclusion criteria: non-diabetic pregnant women living in Winipeg, < 26 weeks' gestation, signed informed consent Exclusion criteria: medical or obstetric contraindications to exercise during pregnancy
Interventions	Intervention group: lifestyle intervention (diet counselling and an exercise program) (n = 112) Intervention included "a community-based exercise program specifically designed for pregnant women was provided". An exercise regimen, 3 to 5 times per week including a weekly exercise session and multiple home sessions of mild-to-moderate exercise for 30 to 45 mins was recommended. Program started between 20-26 weeks. Group exercise sessions including aerobics were held in community centres and instructors were licensed fitness trainers. 2 dietary interviews with counselling were provided Control group: routine care (n = 112).
Outcomes	Primary outcome - prevalence of excessive GWG and measures of physical activity and food intake between the 2 groups. Other measures included physical activity, gestational diabetes, weight-related obstetric procedures, gestational weight gain, the prevalence for LGA and birthweights
Notes	Participants logbooks were collected weekly. Delivery data and maternal weight at delivery were collected from medical records Age (intervention, control): 30.1 [5.2]/28.7 [5.9]. Enrolment gestational age given as < 26 weeks' gestation. Prepregnancy BMI: 24.9 [5.4]/25.7 [5.1]. Authors concluded that a "lifestyle intervention during pregnancy increased physical activity, improved dietary habits and reduced excessive GWG in urban-living pregnant women"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was performed using a computer-generated randomisation allocation table by a staff member without involvement in the study design."
Allocation concealment (selection bias)	Low risk	"After randomisation, participants received a sealed envelope labelled with the assigned randomisation number."
Blinding of participants and personnel (performance bias) All outcomes	High risk	"The study staff were not blinded to the types of intervention."

Hui 2012 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	High risk	"The study staff were not blinded to the types of intervention."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Low risk for primary outcomes - 30 participants (15%) withdrew from the study (7 in intervention group and 23 in the control group). However, only half the women completed dietary logbooks, so these data could not be used
Selective reporting (reporting bias)	Unclear risk	Could not determine.
Other bias	Low risk	None noted. Baseline characteristics comparable.

Hui 2014

Methods	Parallel arm RCT conducted in Winnipeg, Canada between May 2009 and December 2011
Participants	116 normal and high BMI women were randomised (BMI < 25 and BMI > 25), 113 analysed Included if < 20 weeks' gestation, no existing GDM. Excluded if they had medical or obstetric contraindications to exercise during pregnancy
Interventions	Lifestyle intervention (diet counselling and a supervised exercise program) (n = 57) vs control (n = 56). Intervention included "a community-based exercise program specifically designed for pregnant women was provided". An exercise regimen, 3 to 5 times per week including a weekly exercise session and home sessions with DVD instruction of mild to moderate aerobic exercise for 30 to 45 mins was recommended. Program started between 20-26 weeks and continues to 36 weeks. Group exercise sessions including aerobics were held in community centres and instructors were licensed fitness trainers. 2 dietary interviews with dietician counselling using a Food Choice Map were provided (baseline and 2 months later) Control group received standard care.
Outcomes	GWG, birthweight, delivery route, physical activity and food intake, gestational diabetes, LGA
Notes	Investigators stratified results by BMI (< 25 and > 25 kgm ²). Recruitment age: overweight group 31 [4]/32 [5]; normal weight group 31 [3]/29 [6] Gestational age: < 26 weeks. Recruitment BMI: overweight group 29.5 [5.1]/ 29.7 [1.3]; normal weight group 21.6 [2.2]/22.6 [1.9] Authors concluded that "the lifestyle intervention program decreased EGWG, GWG, and offspring birth weight in pregnant women with normal, but not above normal, pre-pregnancy BMI, which was associated with increased physical activity and decreased

	carbohydrate intake“ NCT00486629.	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation table.
Allocation concealment (selection bias)	Low risk	Allocation by a staff member not involved in study design by sealed, numbered envelope
Blinding of participants and personnel (performance bias) All outcomes	High risk	”the study staff were not blinded to the types of intervention.“
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Pregnancy and maternal weight outcomes were collected by student assistants without knowledge of assignment. (High risk for participant logbooks for exercise and diet)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals.
Selective reporting (reporting bias)	Unclear risk	Not able to determine.
Other bias	Low risk	None noted. Baseline characteristics comparable.

Jackson 2011

Methods	RCT, set in 5 prenatal care practices in the San Francisco Bay Area, USA, including 3 public hospitals, 2 academic practices, and a community hospital. 2006-2007
Participants	327 women randomised. Inclusion criteria: English-speaking women 18 years or older and less than 26 weeks of gestation Exclusion criteria: women who report smoking, alcohol use, drug use, or partner violence
Interventions	Intervention group: (163 randomised) The Video Doctor: an interactive computer program including in-depth behavioural risk assessments and tailored counselling messages, and producing printed output for both the patient and clinician. An actor-portrayed Video Doctor appears and offers education on exercise, nutrition and weight gain based on principles of Motivational Interviewing. Dietary counselling focused on increasing intake of fruits and vegetables and whole grains, increasing healthful vs unhealthful fats and decreasing sugary foods. The Video Doctor emphasised dietary and exercise be-

	behaviour changes over weight gain. The Video Doctor programme required 10-15 mins to complete. After 4 weeks, participants received a brief “booster” Video Doctor counselling Control group: (164 randomised) usual care. The usual care group did not interact with the Video Doctor and the program did not produce a Cueing Sheet or Educational Worksheet. Behavioural counselling for the usual care group was determined by the clinician	
Outcomes	Self-reported servings per day or week of healthful foods (e.g. fruits and vegetables) and unhealthful foods (e.g. sweets), and exercise duration and frequency, and weight gain above the IOM guidelines	
Notes	Mean baseline age (intervention, control): 26.1 ± 5.8, 26.9 ± 6.2 Enrolment BMI (intervention, control): reported as % categories: overweight and obese women comprised 48% and 41% of intervention and control groups respectively Gestation (intervention, control): 19.7 ± 5.5, 19.2 ± 6.0.	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by computer.
Allocation concealment (selection bias)	Low risk	Randomisation by computer (interactive computer programme intervention)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants would not have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not stated that staff or outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	6 women were excluded after randomisation: 3 due to insufficient English, 1 because of inaccurate gestational age, and 2 withdrew during the baseline assessment leaving 158 in the Video Doctor group and 163 in the usual care group. ITT analysis was performed for primary outcome (weight gain) for other outcomes 327 were randomised and 287 (88%) completed follow-up
Selective reporting (reporting bias)	Unclear risk	Not able to determine as assessed from published study report

Other bias	Unclear risk	There were no significant differences between the control and Video Doctor groups for any of the demographic variables listed except education. Results for weight gain were not fully reported by randomisation group. Results for mean weight gain of each group were reported without SDs

Jeffries 2009

Methods	RCT, set in a tertiary obstetric hospital in Melbourne, Australia
Participants	Inclusion criteria: pregnant women at < 14 weeks' gestation. Exclusion criteria: age < 18 or > 45 years, type 1 or type 2 diabetes mellitus, multiple pregnancy, or non-English speaking
Interventions	Intervention (n = 125): women allocated to the intervention group were given a personalised weight measurement card, advised of their optimal GWG (based on their BMI at the time of recruitment and the United States IOM guidelines, and instructed to record their weight at 16, 20, 24, 28, 30, 32 and 34 weeks' gestation Control (n = 111): not given instructions about regular weight measurement
Outcomes	Weight gain above IOM guideline, mean weight gain from recruitment to follow-up at 36 weeks' gestation SGA (< 10th centile), large-for-gestational age (> 90th centile), preterm (< 37 weeks), instrumental delivery, caesarean delivery, pre-eclampsias, neonatal hypoglycaemia, shoulder dystocia Weight gain was weight difference between weight at about 36 weeks' gestation and weight at 1st antenatal appointment
Notes	Gestation age at recruitment (intervention, control): 11.6, 11.4 weeks BMI category, n (intervention, control): • underweight (BMI $\leq$ 19.8): 5, 5; • normal (BMI > 19.8, $\leq$ 26.0): 75, 67; • overweight (BMI > 26, $\leq$ 29.0): 20, 18; • obese (BMI > 29.0): 25, 21.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using computer random number generation.
Allocation concealment (selection bias)	Low risk	Using opaque, sequentially numbered envelopes.

Jeffries 2009 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants were blinded to the purpose of the study.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up, 23/148 in intervention group, 27/138 in control group Similar reason of loss to follow-up in intervention and control groups
Selective reporting (reporting bias)	Low risk	The outcomes reported as in the published protocol.
Other bias	Low risk	Baseline characteristics were similar.

Kieffer 2014

Methods	Parallel-arm RCT at community health centre in Detroit, USA from 2004 to 2006	
Participants	General population, 278 randomised, all included in primary analysis Inclusion criteria: pregnant Latinas were eligible if they were age 18 or older, South Detroit residents, and at less than 20 gestation weeks at eligibility screening Exclusion criteria: see inclusion criteria.	
Interventions	Intervention group: a counselling intervention (MOMS intervention included home visits, group classes, related activities and social support from community health workers to influence eating and exercise, weight beliefs and behaviours) (n = 139) Intervention was administered over 11 weeks Control group: routine care (n = 139).	
Outcomes	Dietary behaviour outcomes including sugar, fats, and fibre.	
Notes	Little usable data extracted from this report. Age (intervention, control): 27.3 [5.3]/27.1 [5.1]. Enrolment gestational age < 20 weeks. Recruitment BMI: 24.2 [5.1]/24.7 [5]. Authors concluded that "We confirmed the hypothesis that a community-planned CHW-led healthy lifestyle intervention could improve dietary behaviors of low-income Lantina women during pregnancy"	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Kieffer 2014 (Continued)

Random sequence generation (selection bias)	Low risk	A "statistician generated random allocation sequence in blocks of 40"
Allocation concealment (selection bias)	Low risk	"After baseline data collection, each women received...a sealed envelope containing her group assignment."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants was not feasible.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data collected by trained interviewers who were blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 20% loss to follow-up. Data were available for 139/139 and 136/139 women in the intervention and control groups, respectively, for the primary analysis
Selective reporting (reporting bias)	Unclear risk	Could not determine.
Other bias	Low risk	None noted. Baseline characteristics comparable.

Kong 2014

Methods	RCT at Low State University in USA (accrual dates not stated)
Participants	Obese/overweight pregnant women, 42 randomised. Inclusion criteria: maternal age between 18 and 45 years, singleton pregnancy, non-smoker, self-reported overweight (BMI ≥ 25 kg/m ²) or obese (BMI ≥ 30 kg/m ²) before pregnancy, no prior history of chronic diseases (including type 1 diabetes, cardiovascular disease, thyroid, or lung disorder), and no prior history of gestational diabetes. Only enrolled women with < 3 30-min episodes of physical activity in previous 6 months Exclusion criteria: see inclusion criteria.
Interventions	Intervention group: exercise intervention (unsupervised walking program on treadmill or other setting for a minimum of 150 min/week) (n = 18) Control group: routine care (n = 19).
Outcomes	Activity, weight gain, pregnancy risks and labour procedures, infant birth outcomes
Notes	Women were loaned treadmills for the study. Interventions continued at least to gestational week 35. Data reported separately for overweight (n = 18) and obese (n = 19) participants. Data were collected for 1 week periods at weeks 10-14 (baseline), weeks 17-19 (V2), weeks 27-29 (V3), and weeks 34-36 (V4) Age (obese group: intervention, control): 28.6 [5.3]/25.7 [4]

	Age (overweight group: intervention, control): 26.2 [2.6]/27.3 [3.6] Enrolment gestational age < 15 weeks. Recruitment BMI (obese group: intervention, control): 34.7 [4.6]/34.2 [3.6] Recruitment BMI (overweight group: intervention, control): 26.5 [1.2]/27.4 [1.4] Authors concluded that a "pilot, unsupervised walking intervention increased the moderate-intensity physical activity (MPA) of overweight and obese women during pregnancy" with "trend to more favourable maternal and birth outcomes" in the intervention group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"After the initial enrollment, participants were randomly assigned ...using a computer-based random number generator (Microsoft Excel 2010)."
Allocation concealment (selection bias)	Unclear risk	"All participants and research staff were blinded to the group allocation."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants to intervention was not possible due to the nature of the intervention. Study coordinator not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessor not described. Pregnancy outcome measures self-reported by participants via a postpartum questionnaire and may be subject to bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	9 withdrawals (19.6%, 5 in physical activity group and 4 in control group)
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.
Other bias	Unclear risk	None noted. Baseline characteristics comparable.

Korpi-Hyovalti 2011

Methods	RCT, set in 2 hospitals in rural municipalities (Kauha-joki and Lapua) in Finland
Participants	60 women randomised. Inclusion criteria: women at high risk of gestational diabetes: women had 1 or more risk factors (BMI > 25 kg/m², previous history of GDM or birth of child > 4.5 kg, age > 40 years, family history of diabetes or the venous plasma glucose concentration after 12 hours fasting in the morning was 4.8-5.5 mmol/L and 2-hour OGTT plasma glucose < 7.8 mmol/L

	Exclusion criteria: women who were diagnosed as having GDM in this study and women who had risk factors for GDM or whose fasting venous plasma glucose was 4.8-5.5 mmol/L but who for personal or professional reasons did not wish to participate in the trial	
Interventions	Intervention group: (n = 30) a lifestyle intervention; included diet counselling and exercise counselling. Dietary advice tailored to each woman individually on 6 occasions. Women were encouraged to eat a diet rich in vegetables, berries and fruits, and to use low-fat. Moderate-intensity physical exercise during pregnancy was encouraged, 6 sessions for exercise counselling Control group: close follow-up group (n = 30). All women were given general information on diet and physical activity to decrease the risk of GDM during pregnancy as part of routine care	
Outcomes	Weight gain, GDM, birthweight.	
Notes	Age: 29.2 [5.4]/29.8 [5.4]. Gestation at recruitment given as 8-12 weeks. Baseline BMI: 27.3 [6.0]/25.5 [3.4].	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Women were randomly assigned to the lifestyle intervention group or to the close follow-up group by the study physician in the Central Hospital with the use of a computed randomisation list
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Women were aware of group assignment although it was stated that the nurses scheduling study visits did not have access to the randomisation list. It is not clear what impact the lack of blinding would have on the outcomes measured
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	60 women were randomised, 54 were followed up.
Selective reporting (reporting bias)	Unclear risk	Assessment from published study report.

Other bias	Unclear risk	There were no statistically significant differences in baseline measures between the lifestyle intervention and the close follow-up groups although women in the intervention group had slightly higher prepregnancy weight (mean 76.6 kg compared with 69.6 kg in controls)

Laitinen 2009

Methods	RCT, set in maternal welfare clinics in the city of Turku and neighbouring areas in south-west Finland
Participants	Women were eligible for participation if they were less than 17 weeks' gestation and had no metabolic or chronic diseases such as diabetes Participants were Caucasian.
Interventions	At 1st trimester 256 pregnant women were allocated to 3 groups: modification of dietary intake according to current recommendations with probiotics or placebo and a control group receiving placebo only 1. Control group, (placebo) (n = 85). 2. Intervention group 1 (n = 86) (diet counselling and placebo). 3. Intervention group 2 (n = 85) (diet counselling and probiotics), probiotic capsules containing <i>Lactobacillus rhamnosus</i> GG and <i>Bifidobacterium lactis</i> Bb12. Dietary counselling given by a dietitian at each study visit aimed to modify dietary intake to conform with that currently recommended, particular attention being paid to the quality of dietary fat Study visits took place 3 times during pregnancy at 13.9 (SD 1.6), 23.8 (SD 1.4) and 33.9 (SD 1.4) weeks of gestation and at 1, 6 and 12 months postpartum
Outcomes	Weight gain, energy intake, dietary fibre intake at 3rd trimester of pregnancy Weight gain was calculated by subtracting self-reported prepregnancy weight from that recorded at a prenatal visit or at hospital within 1 week before delivery
Notes	Age (intervention 1, intervention 2, control): 30.1 ± 5.2, 29.7 ± 4.1, 30.2 ± 5.0 Enrolment BMI NR.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Women were randomly assigned to 3 study groups according to computer-generated block randomisation
Allocation concealment (selection bias)	Low risk	Using sealed envelopes. At the 1st study visit the envelopes were opened. The random allocation sequence was thus con-

Laitinen 2009 (Continued)

		cealed until interventions were assigned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Probiotics/placebo were double-blind in the intervention groups but single blind in the control group
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up (to delivery).
Selective reporting (reporting bias)	Low risk	The outcomes reported as in the published protocol.
Other bias	Low risk	No other bias apparent.

Leiferman 2011

Methods	RCT conducted by the Colorado School of Public Health, Denver, USA	
Participants	Pregnant women. Inclusion/exclusion criteria not described.	
Interventions	My Baby My Move (MBMM) was an 8-week community-based program that involved both didactic and experiential components. Peer leaders delivered the program	
Outcomes	Sparse information and no data were available on this trial.	
Notes	Conference abstract only with no usable data. Authors concluded that "These findings suggest that implementing community-based interventions to increase antenatal PA are well received and show promise in ultimately changing PA behaviour" Full report is pending (personal communication). Nodine 2011 is a substudy of 29 women from this study that examined the effect of exercise on sleep parameters	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information on which to base judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient information on which to base judgement.

Leiferman 2011 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information on which to base judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information on which to base judgement.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information on which to base judgement.
Selective reporting (reporting bias)	Unclear risk	Insufficient information on which to base judgement.
Other bias	Unclear risk	Insufficient information on which to base judgement.

Louie 2011

Methods	Parallel-arm RCT conducted in Australia.
Participants	99 randomised, 92 analysed. Inclusion criteria: women with GDM diagnosed by GTT at 20-32 weeks' gestation and singleton pregnancy
Interventions	Dietary intervention: low GI diet (n = 47) vs conventional high-fibre, moderate GI diet (n = 45). Intervention included 3 face-to-face visits with the study dietician
Outcomes	Birthweight, LGA, SGA, caesarean section, macrosomia, GWG.
Notes	Age (intervention, control): 34 [4.1]/32.4 [4.5]. Enrolment gestational age: 26.1 [4]/26 [4.3]. Prepregnancy BMI: 23.9 [4.4]/24.1 [5.7]. Authors concluded that "In intensively monitored women with GDM, an LGI diet and a conventional HF diet produce similar pregnancy outcomes". They suggested that because the intervention began after the 29th week gestation this may have attributed to the lack of difference

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation by "computer-generated numbers, stratified by BMI (BMI < 30 vs $\geq$ 30) and weeks of gestation (< 28 vs $\geq$ 28)"

Louie 2011 (Continued)

Allocation concealment (selection bias)	Low risk	"The allocation sequence was unpredictable and concealed from the recruiter."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"A biostatistician blinded to the diet allocation performed the statistical analyses."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Four women delivered prematurely and three women withdrew after first dietary instruction."
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported.
Other bias	Low risk	Baseline characteristics comparable.

Luoto 2011

Methods	Cluster-RCT, set in primary healthcare centres in 14 municipalities in Pirkanmaa region in south-western Finland
Participants	Recruitment 2007-8. Inclusion criteria: pregnant women at 8-12 weeks' gestation at high risk of developing gestational diabetes; BMI ≥ 25 kg/m² based on measured height and self-reported prepregnancy weight; GDM or any signs of glucose intolerance or newborn's macrosomia (≥ 4500 g) in any earlier pregnancy; type 1 or 2 diabetes in 1st- or 2nd-degree relatives; or age ≥ 40 years Exclusion criteria: at least 1 of the 3 baseline (8-12 weeks' gestation) OGTT measurements was abnormal (fasting blood glucose ≥ 5.3 mmol/L, 10.0 mmol/L at 1 hr, and 8.6 mmol/L at 2 hr); prepregnancy type 1 or 2 diabetes; inability to speak Finnish; age <18 yr; multiple pregnancy; physical restriction preventing physical activity; substance abuse; treatment or clinical history of psychiatric illness
Interventions	Intervention group: (7 municipalities) Individual counselling on physical activity and diet and weight gain. At the 1st visit the recommendations for GWG were discussed and an appropriate weight gain graph was selected to guide the participant in monitoring her weight gain. The primary physical activity counselling was implemented at 8-12 weeks' gestation and the primary dietary counselling session at 16-18 weeks' gestation. Physical activity counselling was enhanced at 4, and diet counselling at 3 subsequent visits Control group: (7 municipalities) usual care group received no counselling beyond usual care, which included some dietary counselling (partly on different topics) and follow-up of gestational weight, but little physical activity counselling
Outcomes	Incidence of GDM as assessed by OGTT (maternal outcome) and newborns' birthweight adjusted for gestational age, maternal weight gain and the need for insulin treatment

	during pregnancy, changes in physical activity and diet (intake of total fat, saturated and polyunsaturated fatty acids, saccharose, and fibre	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The unit of randomisation was municipality. In the randomisation process, participating municipalities were 1st pair-wise matched. 14 municipalities were then randomised by computer
Allocation concealment (selection bias)	Low risk	Cluster-randomised trial with computer randomisation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Women in the intervention group were provided with notebooks to record diet and activity, women in the control group were not; this may have affected recall and may have introduced bias. It was not clear whether staff collecting outcome data were blind to group assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	No loss of clusters (14 clusters were randomised and all were included in the analysis). 343 women in the intervention and 297 in the usual care group agreed to participate in the trial. However, 81 (23.6%) of the participants in intervention group and 93 (31.3%) of the participants in the usual care group had an abnormal OGTT result at baseline and were thus excluded. The final number of participants in the analyses was 219 (89.0% of participants receiving allocated intervention) in the intervention group and 180 (91.8% of participants receiving allocated intervention) in the usual care group. However about 40% of eligible participants of each group were followed up

Selective reporting (reporting bias)	Unclear risk	Assessment from published study reports. Analysis appropriate for clusters. There was adjustment of data for clustering and various cluster, clinic and individual level differences at baseline
Other bias	Unclear risk	Baseline characteristics of each group were similar, except that women in the intervention group had higher education than in the usual care group

Magee 1990

Methods	RCT, set in prenatal care at the University of Washington Obstetrics Clinics
Participants	Pregnant women with obesity (prepregnancy weight > 120% of ideal body weight) and diagnosed with gestational diabetes, recruited at 28 weeks' gestation
Interventions	All women were hospitalised for 2-week duration in the metabolic ward Intervention: calorie-restricted (n = 7): during the 1st week, the women consumed normal diet with 2400 kcal/day; 50% CHO, 30% fat and 20% protein with 11 g of total dietary fibre per 500 kcal. During the 2nd week, the women were placed on 1200 kcal/day diet. This reduction was accomplished by decreasing portion sizes without changing other features of diet Control (n = 5): during the 1st week, the women consumed identical diet as the intervention group; 2400 kcal/day, and continued on the same diet (2400 kcal/day) during the 2nd week
Outcomes	Metabolic indices: fasting plasma glucose, OGTT, insulin, triglyceride, free fatty acids, glycerol, β -hydroxybutyrate, and urine ketones We have not included outcome data from this hospital inpatient study in the analyses in the review
Notes	Age (calorie-restricted, control): 30 $\pm$ 4, 36 $\pm$ 5 years.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided.

Magee 1990 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided.
Selective reporting (reporting bias)	Unclear risk	Could not determine.
Other bias	Unclear risk	No information provided.

Marcinkevage 2012

Methods	RCT in a large urban hospital in the USA.	
Participants	High risk (obese and overweight), 55 randomised, 36 analysed so far (ongoing) Inclusion criteria: overweight and obese 'minority' women receiving prenatal care. Gestation at recruitment: 14.4 +-2.8 Exclusion criteria: see inclusion criteria.	
Interventions	Intervention group: lifestyle intervention (monthly behavioural counselling meeting focused on reducing sedentary behaviour and increasing levels of physical activity) (n = 17) Control group: routine care (n = 19).	
Outcomes	Physical activity, GWG, glucose values.	
Notes	Abstract only with no usable data. Preliminary analysis shows decrease in median(range) total activity in both groups from first visit to mid-pregnancy. Reduction in sedentary behaviour from first trimester to mid-pregnancy in intervention but not regular group. Median(range) GWG at mid-pregnancy is similar for both groups. At mid-pregnancy lower fasting and 30 min glucose values in intervention vs regular care. Preliminary data demonstrate the feasibility of modifying lifestyle during early pregnancy in underserved black women Authors concluded that "Preliminary data demonstrate the feasibility of modifying lifestyle during early pregnancy in underserved black women"	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described. "randomly assigned".
Allocation concealment (selection bias)	Unclear risk	Not described.

Marcinkevage 2012 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information.
Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Insufficient information.

Moses 2009

Methods	Randomised controlled trial, set in the city of Wollongong, New South Wales, Australia
Participants	Inclusion criteria: pregnant women, age 18-40 years (inclusive), singleton pregnancy, no previous GDM, nonsmoker, diagnosis of GDM and seen for the 1st dietary visit between 28 and 32 weeks of gestation, and ability to follow the protocol requirements Exclusion criteria: any condition or medication that could affect glucose levels and unwillingness to follow the prescribed diet
Interventions	63 women were randomly assigned to receive 1 of 2 different diets, low-GI diet (n = 31) or higher-GI diet (n = 32). Both diets were compatible with the recommended nutritional intake in pregnancy. The CHO intake was designed to achieve a minimum of 175 g/day with only the recommended choice of CHO foods varying. The dietary advice by dietitian was individualised with specific mention of the energy and nutrient balance to achieve normal weight gain during the 3rd trimester The low-glycaemic diet: based on previously verified low-GI food, including pasta, grain breads, and unprocessed breakfast cereals with a high fibre content. Women were specifically asked to avoid consuming white bread, processed commercial breakfast cereals, potatoes, and some rice varieties The higher-glycaemic diet: a diet with a high-fibre and low-sugar content, with no specific mention of the GI. Potatoes, whole wheat bread, and specific high-fibre, moderate-to-high-GI breakfast cereals were recommended
Outcomes	Induction of labour, method of delivery, LGA baby (> 90th centile), SGA baby (< 10th centile)
Notes	Age (LGI, HGI): 30.8 + 0.7, 31.3 + 0.8. Gestational age at entry to study (LGI, HGI): 30.3 + 0.2 weeks, LGI 29.9 + 0.2 weeks BMI at enrolment (LGI, HGI): 32.0, 32.8 kg/m ² .

Risk of bias

Moses 2009 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Women were randomly assigned using permuted blocks of unequal size with the list generated using STATA (version 7.0)
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The physician caring for the women was blinded. Study dietitians were not blinded to dietary assignment but were aware of the need for impartiality and equivalent treatment Participants were impossible to blind to the GI concept, as it is widely known and discussed in the lay press
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropout apparent.
Selective reporting (reporting bias)	Unclear risk	Could not determine.
Other bias	Low risk	There were no significant differences in the baseline characteristics of the 2 groups

Moses 2014

Methods	Parallel-arm RCT conducted in Australia from Feb 2010 to Sept 2012
Participants	691 randomised, 576 analysed. Inclusion: healthy pregnant women at 12 to 16 weeks' gestation who agree to be randomised Exclusion: women with pregestational diabetes; multiple birth; assisted reproduction; special diet or referred to a dietitian for other reasons
Interventions	A low glycaemic diet (n = 354) or a conventional healthy diet (n = 337) from 12 to 16 weeks' gestation for the remainder of pregnancy
Outcomes	Primary outcomes: prevalence of LGA at birth (more than 90th centile); prevalence of childhood obesity as determined by BMI Secondary outcomes: prevalence of gestational diabetes; ponderal index; prevalence of SGA; GWG

Notes	Age (intervention, control): 29.9 [0.3]/29.9 [0.3]. Enrolment gestational age: 16.5 [0.1]/16.2 [0.1]. Prepregnancy BMI: 24.3 [0.3]/24.7 [0.3]. Outcomes were assessed at baseline, 28 weeks and 34 weeks. Authors concluded that "A low-intensity dietary intervention with an LGI diet compared with an HE diet in pregnancy did not result in any significant differences in birth weight, fetal percentile, or PI. In conclusion, the outcome of this study was neutral. Infants of women instructed to consume LGI CHO foods during pregnancy were of normal size and had a similar PI to those of infants of women who received conventional HE advice"	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned."
Allocation concealment (selection bias)	Unclear risk	"Randomly assigned."
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Study personnel were not blinded to the dietary assignment but were aware of the need for impartiality and equivalent treatment. Obstetric care providers were not specifically blinded to the study allocation but were also not informed."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout < 20%. In the low GI group, 58 women were later excluded (27 women had developed GD). In the HE group, 57 women were later excluded (28 women had developed GD)
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported.
Other bias	Low risk	None noted. Baseline characteristics comparable.

Mujisindi 2014

Methods	RCT (setting not mentioned) in USA (accrual dates NR).
Participants	High risk (obese and overweight), 79 randomised. Inclusion criteria: overweight and obese 'minority' women receiving prenatal care Exclusion criteria: see inclusion criteria.
Interventions	Intervention group: lifestyle intervention (behaviour counselling with 5 dietary/nutrition consultations during pregnancy and at 3 months postpartum, food records, pedometers and logs, pregnancy activity questionnaire and food frequency questionnaire) (n = ?) Control group: routine care (n = ?).
Outcomes	Primary outcome was GWG and postpartum weight retention rates. Secondary outcomes included obstetric, delivery and neonatal outcomes
Notes	Abstract only with no usable data. Obese women enrolled in a structured nutrition program during pregnancy and in the postpartum period had similar GWG and postpartum weight retention to women in standard care. There was no difference in demographic data, parity, smoking status and socioeconomic status. When comparing the PEN vs STD groups, there was no difference in mean GWG at 20 weeks, 24, 30 and 36 weeks. Return to study entry weight was compared between the groups at 3 and 6 months. There was no difference between the groups at either time (P = 0.21 and 0.18 respectively) Authors concluded that "Obese women enrolled in a structured nutrition program during pregnancy and in the postpartum period had similar gestational weight gain and postpartum weight retention as women in standard care"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described. "Randomly assigned."
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information.
Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Insufficient information.

Murtezani 2014

Methods	A parallel arm RCT conducted in the Republic of Kosovo. Accrual dates not given
Participants	72 pregnant women randomised, 63 analysed.
Interventions	Intervention (n = 30) involved an exercise training program that started in the second trimester and was continued until the end of pregnancy. Each session consisted of 40-45 min of aerobic and strength exercise. Individuals were supervised by certified aerobic-instructors, and each session included a maximum of 10 participants. Intensity was moderate to vigorous; supine postures and Valsalva manoeuvres were avoided Controls had routine care (n = 33).
Outcomes	GWG, neonatal weight, Apgars, macrosomia.
Notes	The participants were examined twice during the study period. The first visit was between 14-20 weeks of gestation (baseline visit) and the second at week 36-38 (after the intervention) Recruitment age: 26.9 [4.7]/25.7 [5.1]. Recruitment gestation: 18.9 [1.8]/ 18.3 [1.4]. Prepregnancy BMI: 23 [2.6]/ 22.4 [2.2]. "Supervised aerobic and strength conditioning exercise performed over the second and third trimester does not have a negative impact on the newborn's size and health." Reported gestational weight, not weight gain.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random assignment procedure was performed using random numbers generated by a computer program
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Report states 'single blind' but details not provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Report states 'single blind' but details not provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	9 participants (4 from the control group and 5 from the intervention group) withdrew after randomisation for medical and personal reasons: hypertension (n = 2), vascular disease (n = 1), intrauterine growth restriction (n = 1), amniotic-fluid leakage (n = 2), premature birth (n = 1) , injured n = 1) and unknown (n = 1). It was not

		stated from which group these withdrawals occurred
Selective reporting (reporting bias)	High risk	Women with hypertension, preterm birth and amniotic fluid leakage were excluded after randomisation, yet these are potential side effects of vigorous exercise in pregnancy
Other bias	High risk	Baseline characteristics were similar for study groups. Women with hypertension, preterm birth and amniotic fluid leakage were excluded after randomisation, yet these are potential side effects of vigorous exercise in pregnancy and needed to be reported

Nascimento 2012

Methods	RCT conducted at an antenatal outpatient clinic in Brazil from August 2008 to March 2010
Participants	High risk. Overweight or obese, 82 randomised. Inclusion criteria: pregnant women ≥ 18 yrs, pre-gestational BMI ≥ 26 kg/m ² , gestational age 14-24 weeks Exclusion criteria: multiple pregnancy, exercising regularly, and conditions that contraindicate exercise, such as cervical incompetence, severe arterial hypertension, diabetes with vascular disease and risk of abortion
Interventions	Intervention group: supervised exercise program (n = 40). Intervention consisted of an exercise program guided by a trained physical therapist in weekly classes with light to moderate intensity exercise for 40 mins. It also included home exercise counselling which was to be performed 5 times per week (consisting of a sequence of 22 exercises or walking) Control group: routine prenatal care program (n = 42).
Outcomes	Primary outcomes were GWG and excessive weight gain. Secondary outcomes were increased arterial blood pressure, perinatal outcomes and QoL (WHOQOL)
Notes	Outcomes measured at baseline and 36 weeks. Delivery data were collected from medical records Age (intervention, control): 29.7 [6.8]/30.9 [5.9]. Enrolment gestational age (intervention, control): 14.3 [4.5]/13.6 [3.5] Prepregnancy BMI: 34.8 [6.6]/36.4 [6.9]. Slight baseline imbalances noted as 8/40 vs 15/42 were diabetic and 15/40 vs 22/42 were hypertensive in exercise and control groups, respectively, at baseline Authors concluded that "The exercise programme was not associated with control of gestational weight gain in our sample as a whole, but was beneficial for lower gestational weight gain in overweight women. Exercise was not associated with adverse perinatal outcomes and did not affect variation in arterial blood pressure or the perception of

QoL ^a		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomised to the groups using the SAS statistical program (SAS Institute, Cary, NC, USA), which generated a list of random numbers based on a uniform distribution."
Allocation concealment (selection bias)	Low risk	"The sequence was randomly distributed in opaque envelopes, which were sealed and sequentially numbered. Each participant received a sequence number corresponding to a sealed envelope."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 woman in each group withdrew. For neonatal weight outcome, missing data were > 20% but similar numbers missing in each group. Authors indicate that this was because some women delivered at other hospitals
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported.
Other bias	Unclear risk	Baseline imbalances noted as 8/40 vs 15/42 were diabetic and 15/40 vs 22/42 were hypertensive in exercise and control groups, respectively, at baseline. Also, the control group had a greater proportion of obese women. This could affect some outcomes (e.g. LGA, GWG) in favour of the intervention

Oostdam 2012

Methods	RCT at hospitals and midwifery practices in The Netherlands from January 2007 to January 2011
Participants	High risk. Overweight or obese, 121 randomised, 101 analysed Inclusion criteria: pregnant women who were overweight or obese and at risk for GDM. AND had at least 1 of the 3 following characteristics: (1) history of macrosomia. (2) history of GDM; or (3) first-grade relative with Type 2 diabetes Exclusion criteria: recruitment after 20 weeks of gestation; age under 18 years; non-Dutch speaker; having been diagnosed with GDM before randomisation; hypertension; alcohol abuse; drug abuse; use of any medication that affects insulin secretion or insulin sensitivity; serious pulmonary, cardiac, hepatic, or renal impairment; malignant disease; and serious mental or physical impairment
Interventions	Intervention group: exercise intervention (2 sessions of aerobic and strengthening exercises per week; each exercise session lasted for 60 mins) (n = 62) Control group: routine care (n = 59).
Outcomes	Maternal outcome measures were fasting blood glucose (mmol/L, fasting insulin (pmol/L) and HbA1c (%), body weight (kg), BMI (kg/m ²), and daily physical activity (min/week). Offspring outcome measures were birthweight and fetal growth
Notes	Outcomes assessed at baseline, 24 and 32 weeks. Age (intervention, control): 30.8 [5.2]/30.1 [4.5]. Enrolment gestational age was 15 weeks. Prepregnancy BMI: 33 [3.7]/33.9 [5.6]. Authors concluded that exercise intervention "had no effects on fasting blood glucose, insulin sensitivity, and birthweight, most probably because of low compliance"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation, stratified by hospital.
Allocation concealment (selection bias)	Low risk	"Women were recruited by midwives and gynaecologists who were unaware of the allocation of other women, with no risk of compromising allocation concealment."
Blinding of participants and personnel (performance bias) All outcomes	High risk	"By the nature of the intervention the researcher and research assistant could not be blinded for allocation after randomisation."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All outcome measures were assessed by independent examiners, unaware of group allocation."

Oostdam 2012 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	High dropout rates, especially at 32 weeks (19/62 [31%] did not respond in intervention group and 12/59 [20%] did not respond in control group). For GWG outcome dropout rate was 31% overall
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported.
Other bias	High risk	Poor adherence to the intervention - "only a small proportion (16.3%) of the women in our intervention group attended at least half of the training sessions" Follow-up weight gain data were collected at 32 weeks (much earlier than most other included studies)

Petrella 2013

Methods	RCT in Italy (setting and accrual dates NR).	
Participants	High risk. Overweight or obese. 61 randomised. Inclusion criteria: women with BMI > 25 at 1st trimester, > 18 years with singleton pregnancy at 12 weeks' gestation. Exclusion criteria: women with twin pregnancy, chronic disorders, GDM in previous pregnancy, smoking, previous surgery, women who engaged in regular physical activity, or used dietary supplements or herbal products known to affect body weight were excluded	
Interventions	Intervention group: lifestyle intervention involving a caloric restricted low GI diet (1500 kcal/day) and prescribed moderate-intensity exercise 30 min/day, 3 times per week. Pedometers were to be worn (n = 33) Control group: routine care with a nutritional brochure about health eating (n = 28)	
Outcomes	GDM, GWG, hypertension, and preterm delivery.	
Notes	Recruitment age: 31 [4.2]/32.4 [5.9]. Gestational age: first trimester. Recruitment BMI: 32.1 [5]/ 32.9 [6.2]. Authors concluded that "A constant physical activity and a change toward healthy eating improves nutrients intake, prevents excessive weight gain and avoids the maternal unfavorable outcomes associated with overweight/obese women"	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation in blocks of 3.

Petrella 2013 (Continued)

Allocation concealment (selection bias)	Low risk	"Study randomization is numbered and sealed in white envelopes. Randomization occurs in consecutive order at time of the first visit."
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Due to study design, both gynecologist and dietitian know the allocation of the patient."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessor knew the allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 2 women in the control group withdrew.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported.
Other bias	Low risk	Baseline characteristics similar.

Petrov Fieril 2014

Methods	RCT conducted at 2 ANCs in Gothenburg, Sweden with recruitment from Feb 2006 to Nov 2006 and Sept 2008 to April 2009
Participants	92 pregnant women randomised, 72 analysed. Included if singleton pregnancy < 14 weeks' gestation, no medical or obstetric complications, ability to understand Swedish Excluded if contraindications to exercise in pregnancy.
Interventions	Intervention group received supervised resistance exercise twice a week, with light barbells and weight plates in a group setting, performed at an activity level equivalent to within moderate-to-vigorous between weeks 14 to 25 gestation, and was self-adjusted (n = 51). In addition, walking, cycling, water-gymnastics, Pilates, yoga and home exercises that included pelvic floor training were recommended. Controls received a generalised exercise recommendation, a home-based training program and a telephone (n = 41)
Outcomes	Health-related quality of life, physical strength, pain, weight, blood pressure, functional status, activity level and perinatal data
Notes	Little usable review data (birthweight only). Age (intervention, control): 30.8 [3.6]/30.6 [3.4]. Enrolment gestational age: 13 weeks. Prepregnancy BMI: 22.6 [2.5]/23 [2.6]. Authors concluded that "supervised, moderate-to vigorous resistance exercise does not jeopardize the health status of healthy pregnant women or the fetus"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"participants were randomly assigned to either the intervention group or the control group (allocation ratio 1:1)", however the group sizes were significantly different (51 vs 41, respectively)
Allocation concealment (selection bias)	Low risk	"The research coordinator performed the randomization by using opaque sealed envelopes, which were randomly picked out before the meeting with each participant."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All data were collected at a primary health care location by an investigator who was blinded to" group allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	25% and 18% of participants dropped out of the intervention and control groups, respectively
Selective reporting (reporting bias)	Unclear risk	Protocol not seen. GWG and EGWG NR.
Other bias	Low risk	Baseline characteristics were similar in study groups.

Phelan 2011

Methods	RCT, 2 arms with individual randomisation stratified by prepregnancy weight, set in 6 obstetric offices in Providence, Rhode Island, USA from 2006 to 2008
Participants	401 women randomised. Inclusion criteria: gestational age between 10 and 16 weeks, BMI between 19.8 and 40, nonsmoking , adults (aged > 18 yr), fluency in English, access to a telephone, and a singleton pregnancy Exclusion criteria: major health or psychiatric diseases, weight loss during pregnancy, or a history of ≥ 3 miscarriages
Interventions	Intervention group: standard care plus a behavioural lifestyle intervention. The Fit for Delivery intervention included a face-to-face visit with an interventionist at the onset of treatment who discussed appropriate weight gains during pregnancy, physical activity (30 min of walking most days of the week), and calorie goals (20 kcal/kg); emphasis was placed on decreasing high fat foods, increasing physical activity, and daily self-monitoring of eating, exercise, and weight. Body-weight scales, food records, and pedometers

	were provided to promote adherence to daily self-monitoring. Automated postcards that prompted healthy eating and exercise habits were mailed weekly. In addition, after each clinic visit, women were sent personalised graphs of their weight gains with feedback. All women in the intervention received 3 brief (i.e. 10-15 min) supportive phone calls from the dietitian during the intervention. Women who were over- or under weight-gain guidelines during any 1 month interval received additional brief, supportive phone calls (2 calls/month) that provided structured meal plans, and specific goals until weight gains returned to appropriate amounts Control group: routine care. Women received standard nutrition counselling provided by physicians, nurses, nutritionists, and counsellors. As part of routine care women were weighed by nurses at each clinical visit; weight graphs were not provided	
Outcomes	Excessive weight gain, low weight gain, preterm birth, pre-eclampsia or eclampsia, caesarean delivery rate, high birthweight, low birthweight, maternal weight retention	
Notes	Baseline age (intervention, control): 28.8 ± 5.2, 28.6 ± 5.2 Baseline BMI (intervention, control): 26.48 ± 5.9, 26.32 ± 5.6 Enrolment gestation (intervention, control): 13.5 ± 1.8, 13.6 ± 1.8	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computer-generated in randomly varying block sizes and stratified by clinic and BMI category
Allocation concealment (selection bias)	Low risk	Allocation was concealed in opaque envelopes prepared by the study statistician
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unblinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	In the abstract it was stated that outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up 34 in the standard care group, 36 in the intervention group. Exclusions: 18 in the standard care group, 25 in the intervention group 401 participants were randomly assigned into the intervention (n = 201) and control groups (n = 200), included in 6 month postpartum analysis; 182 control, 176 in-intervention ITT analysis was performed assuming that those lost to follow-up were treatment fail-

Phelan 2011 (Continued)

		ures. It was reported that this revealed almost identical results as for those completing the study (data not shown)
Selective reporting (reporting bias)	Unclear risk	Assessment from published study report.
Other bias	Unclear risk	The 2 study groups did not significantly differ on key baseline measures (sample stratified)

Pinzon 2012

Methods	RCT conducted in Colombia with recruitment from March 2008 to November 2009	
Participants	General population. 64 women randomised. Inclusion criteria: nulliparous women in gestational week 16-20 with live fetus and normal pregnancy Exclusion criteria: history of high BP, chronic illness, persistent bleeding after 12 weeks' gestation, poorly-controlled thyroid disease, placenta praevia, incompetent cervix, oligo-hydramnios, miscarriage in previous 12 months	
Interventions	Intervention group: exercise intervention (n = 33) involved a supervised exercise program 3 times a week for 12 weeks. Exercise sessions involved walking (10 min) aerobic exercise (30 min), stretching (10 min) and relaxation exercise (10 min) Control group: usual activities (n = 31).	
Outcomes	Fitness (VO2 max, BP, heart rate at rest, and other parameters) changes in blood lipids, insulin sensitivity (HOMA-IR) and body composition (fat-free mass, body fat, skinfold thickness and muscular area), maternal weight, birthweight, neonatal outcomes	
Notes	Age (intervention, control): 19.2 [2.6]/19.5 [3.4]. Enrolment gestational age: 17.5 [3.4]/17 [4.5]. Recruitment BMI: 21.4 [2.4]/22.4 [3.8]. "Regular aerobic exercise improves endothelium-dependent vasodilation in pregnancy. " (Ramirez-velez 2011) "At the end of the 3-month program, there was no difference in the change in blood lipids. Triglycerides and VLDL were significantly lower in the experimental group. The experimental group showed lower values of body fat and skinfold thicknesses than did the control group, but these differentials were non-significant. " (Pinzon 2012) There was no significant difference between groups regarding maternal weight gain during pregnancy Authors concluded that "The potential public health benefits of exercise are to great and this study supports existing guidelines indicating that latina women may begin or maintain an exercise program during pregnancy"	

Risk of bias

Bias	Authors' judgement	Support for judgement

Pinzon 2012 (Continued)

Random sequence generation (selection bias)	Low risk	"computer-generated randomisation list."
Allocation concealment (selection bias)	Low risk	Sequentially numbered sealed opaque envelopes. "The treatment allocation system was set up so that the researcher in charge of randomly assigning participants to each group did not know in advance which treatment the participant was going to receive."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" "research assistants were blinded to the group assignment of the subjects and were in charge of the prenatal care of the women". "Due to the nature of the study, it was not possible to blind the women participating."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"all study measurements were done by a person blinded to the distribution of the patients."
Incomplete outcome data (attrition bias) All outcomes	High risk	14 women withdrew early (22%; 9 in study and 5 in control arm) therefore 50/64 women assessed for fitness outcomes. Weight and pregnancy outcome data were only available for 35/64 women (55%; 18 in study and 17 in control group)
Selective reporting (reporting bias)	Unclear risk	Unable to comment as study protocol not seen.
Other bias	Low risk	None noted. Adherence was 75%. Baseline characteristics were similar

Pollak 2014

Methods	Pilot RCT with ratio 2:1, conducted in 2 antenatal clinics in USA in 2012
Participants	35 overweight and obese women randomised. Included if 18 years or older, English-speaking, registered for prenatal care at participating clinics, pre-pregnancy BMI of 25-40, 12-21 weeks' gestation, and having a cell phone with an unlimited texting plan for the next 5 months Excluded if pre-existing diabetes, limited mobility or inability to walk, impaired cognition or mental health with inability to provide consent

Interventions	SMS texting intervention (n = 22) targeting weight-related behaviours including increasing daily steps to 10000, avoiding sweetened drinks, eating 5 fruit and veg per day, and eliminating fast food intake. Tests were sent 3 times per week and women were asked to text back their self-monitored weight measurement Control intervention (n = 11) was a general 'text4baby' intervention with general information about pregnancy with few tests related to healthy eating or physical activity Women were asked to wear a pedometer.
Outcomes	Weight at 40 weeks, eating habit scores, physical activity scores Follow-up surveys were conducted at approximately 22 and 32 weeks' gestation and women weighed. In addition, weights were obtained from clinical records from baseline and delivery
Notes	No usable data for this review. The main results were that mean weight gain in the intervention group was estimated to be 6 pounds less than the control group at 40 weeks' gestation for women who completed the intervention (n = 23) Mean age: 29 vs 32 years. Gestation at recruitment: 16 vs 17 weeks. Pre-pregnancy BMI: 29 vs 28 kg/m². Investigators concluded that "SMS texting is a promising vehicle for behavior change among pregnant women"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomized eligible women in a 2:1 fashion."
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	10 women withdrew from the study; however, their weight data from clinical records were included (ITT analysis). 2 others miscarried and were excluded
Selective reporting (reporting bias)	Unclear risk	Protocol not seen but no usable (extractable) outcome data were provided in the report

Other bias	Low risk	Baseline characteristics were similar.

Polley 2002

Methods	RCT, set in an obstetric clinic for low-income women at a hospital in Pittsburgh, PA, USA
Participants	Inclusion criteria: pregnant women before 20 weeks of gestation. (Women were recruited in to 4 cells; normal and overweight, black and white.) Exclusion criteria: underweight women, younger than 18 years, 1st prenatal visit > 12 weeks' gestation, high-risk pregnancy (i.e. drug abuse, chronic health problems, previous complications during pregnancy, current multiple gestation)
Interventions	Intervention (n = 57): the intervention was provided at regular scheduled clinic visits by staff with training in nutrition or clinical psychology. Education about weight gain, healthy eating, and exercise and individual graphs of their weight gain Shortly after recruitment, written and oral information were given in the following area: appropriate weight gain, exercise, healthy eating. Newsletters prompting healthy eating and exercise habits were mailed bi-weekly. After each clinic visit, women were sent a personalised graph of their weight gain Those exceeding weight gain goals were given additional individualised nutrition and behavioural counselling using the format listed; a stepped care approach Control (n = 53): usual care: standard nutrition counselling provided by the physicians, nurses, nutritionists and WIC counsellors. This counselling emphasised a well-balanced dietary intake and advice to take a multivitamin/iron supplement
Outcomes	Excessive weight gain, total weight gain, low weight gain. Low birthweight infants, macrosomia infants, preterm delivery, caesarean delivery, pre-eclampsia, weight retention at 4 weeks' postpartum Total weight gain was based on self-reported prepregnancy weight and weight at last clinic visit prior to delivery
Notes	Excessive weight gain categorised as above the IOM recommendations Low weight gain categorised as below the IOM recommendations IOM recommends a weight gain of 6.8-11.3 kg for overweight women (BMI of 26-29) and a weight gain of 6.8 kg (with no specified upper limit) for obese women (BMI > 29) Age of participants 25.5 ± 4.8. Gestational age at recruitment (intervention, control): 14.7 ± 3.1 weeks BMI category, n (intervention, control): - normal weight (BMI 19.8-26): 30, 31; - overweight (BMI > 26): 27, 22.

Risk of bias

Bias	Authors' judgement	Support for judgement

Polley 2002 (Continued)

Random sequence generation (selection bias)	Unclear risk	Women were randomly assigned to the standard care control group or to the intervention
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Using ITT approach. Loss to follow-up < 10%.
Selective reporting (reporting bias)	Unclear risk	Could not determine.
Other bias	Unclear risk	Refusal rates were higher among black women (28/74 refused) than among white (16/90 refused), and higher in overweight black women than in any of the other 3 weight-by-race categories

Poston 2013

Methods	A pilot RCT conducted at multiple tertiary and university hospitals in the UK with recruitment from March 2010 to May 2013. (UPBEAT study)
Participants	183 randomised, 154 analysed. Inclusion criteria: BMI ≥ 30 kg/m ² and singleton pregnancy; gestational age > 15 weeks and < 17 weeks' gestation Exclusion criteria: unable or unwilling to give written informed consent; gestation < 15 weeks and > 17 weeks, pre-existing diabetes, pre-existing hypertension (treated), pre-existing renal disease, multiple pregnancies; systemic lupus erythematosus antiphospholipid syndrome, sickle cell disease, thalassaemia, coeliac disease, currently prescribed metformin, thyroid disease or current psychosis
Interventions	Intervention group: a lifestyle intervention (diet plus exercise) (n = 94) involving 1 1-to-1 session with a health trainer and then weekly group sessions for 8 consecutive weeks from 19 weeks' gestation. Sessions delivered by health trainers involved diet and exercise advice informed by psychological models of health behaviour. Dietary advice focused on increased consumption of foods with a low dietary GI, and reduction of saturated fats. Physical activity advice encouraged women to increase daily walking activity at moderate intensity level, setting goals monitored by a pedometer. Women also received a DVD of a pregnancy specific exercise regimen Control group: routine care (n = 89).

Poston 2013 (Continued)

Outcomes	Primary outcome: GDM. Others were GWG, macrosomia, LGA, dietary and exercise parameters, anxiety and depression
Notes	Age (intervention, control): 30.4 [5.7]/30.7 [4.9]. Enrolment gestational age was 16 weeks. Recruitment BMI: 36.5 [4.7]/36.1 [4.8].

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was performed online" "balanced by minimisation for maternal age, centre, ethnicity, parity and BMI."
Allocation concealment (selection bias)	Low risk	"randomised treatment was allocated automatically" by online randomisation program
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	14 women (15.7%) dropped out of the control arm, and 15 lost to follow-up in the intervention group (15.8%)
Selective reporting (reporting bias)	Unclear risk	Prespecified outcomes reported, except for GWG. ITT analysis
Other bias	Low risk	Baseline characteristics were comparable.

Price 2012

Methods	RCT at local obstetric practices in Austin, Texas, in USA from July 2006 to March 2010
Participants	General population, 91 randomised, 62 analysed. Inclusion criteria: sedentary women 12-14 weeks' gestation; viable singleton pregnancy at 12-14 weeks by reasonable dates and/or ultrasound; body mass index (BMI) less than 39 kg/m ² Exclusion criteria: no aerobic exercise more than once per week for at least the past 6 months; chronic heart or lung disease; poorly controlled diabetes, hypertension, epilepsy, or hyperthyroidism; severe anaemia no orthopedic limitations; and history of premature delivery, infant delivered for SGA, or unexplained fetal death

Interventions	Intervention group: exercise intervention (n = 43). Exercise intervention involved a program of supervised aerobic training (45-60 mins, 4 days a week) Control group: sedentary women (n = 48). "Control subjects were told not to exercise."
Outcomes	Cardiorespiratory fitness. Strength, flexibility, and discomfort. Pregnancy complications, delivery data, postpartum recovery
Notes	Outcomes assessed at 5 points: 12-14 weeks, 18-20 weeks, 24-26 weeks, 30-32 weeks, and 6-8 weeks postpartum Age (intervention, control): 30.5 [5]/27.6 [7.3] (P = 0.08). Enrolment gestational age was at 12-14 weeks. Prepregnancy BMI: 26.6 [3.1]/28.7 [5.4] (P = 0.042). "Previously sedentary women who began exercising at 12-14 weeks had improved fitness and delivery outcomes." Authors concluded that "Compared with women who remained sedentary, active women improved aerobic fitness and muscular strength, delivered comparable size infants with significantly fewer cesarean deliveries, and recovered faster postpartum, at least related to the lower incidence of cesarean section. Active women developed no gestational hypertension and reported no injuries related to the exercise regimen"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned."
Allocation concealment (selection bias)	Low risk	"Subjects were randomized using numbered, opaque envelopes containing an equal number of group assignments prepared by the study statistician."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded. "Author kept a log of attendance" and seemed to perform the fitness assessments
Incomplete outcome data (attrition bias) All outcomes	High risk	12/43 (28%) and 17/48 (35%) dropped out in the intervention and control groups, respectively. Reasons for drop outs in intervention group were logistics (9) and other reasons (3). Reasons in control group were immediate withdrawal due to wanting to exercise (5), and later withdrawal due to

		wanting to exercise (3) and logistics (9)
Selective reporting (reporting bias)	Unclear risk	Mean weight gain (12.4 kg vs 10.5 kg in intervention and control groups, respectively) was NR with standard deviations or denominators so these data were not usable in our meta-analysis
Other bias	High risk	Baseline BMI was significantly lower in the intervention group and loss to follow-up was high. Also, "control subjects were told not to exercise because it would blur the distinction between the groups". This contributed to high drop out rates in the control group and may make results less generalisable by enforcing no exercise. This study design seems ethically flawed

Quinlivan 2011

Methods	RCT set in the maternity service of a public general hospital serving a socio-economically disadvantaged area in Melbourne, Australia	
Participants	132 randomised. Inclusion criteria: pregnant with a fetus with no known anomalies, spoke English, did not intend to relinquish their infant, did not have a multiple gestation, were able to attend hospital for antenatal care and were overweight (BMI 25-29. 9) or obese (BMI > 29 .9) Exclusion criteria: not described.	
Interventions	Intervention group: a 4-step multidisciplinary protocol of antenatal care which had the following 4 criteria: (i) continuity of care provider; (ii) weighing on arrival; (iii) brief dietary intervention by a food technologist at every antenatal visit; and (iv) psychological assessment. Women attended special study clinics Control group: routine care (with access to high-risk clinics if medically indicated)	
Outcomes	Weight gain, preterm delivery.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation to the intervention or control groups occurred using computer-generated sequence

Allocation concealment (selection bias)	Low risk	Numbered sealed opaque envelopes, stratified by category (overweight or obese;16), which were only opened by the midwife after each woman's enrolment was completed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome data for mother and infant were audited by a nurse independent of clinical care pathways and blinded to randomisation status
Incomplete outcome data (attrition bias) All outcomes	Low risk	132 randomised, 124 analysed (8 excluded from analysis (4 of each group)
Selective reporting (reporting bias)	Unclear risk	Assessment from published study report.
Other bias	Unclear risk	There were no significant differences in terms of antenatal, demographic and health behaviour variables between intervention and control groups. Women in the intervention group attended special study clinics; these clinics may have been different from standard clinics in more ways than the intended study interventions (although it was stated that care was standard apart from the 4 stage intervention)

Rae 2000

Methods	RCT, set in the Diabetes Service, King Edward Memorial Hospital for Women, Perth, Western Australia
Participants	Inclusion criteria: gestation < 35 weeks and 6 days, > 110% of ideal body weight for height (adjusted for expected pregnancy weight gain and using a BMI of 25 as equal to 100% ideal body weight), OGTT with fasting plasma glucose > 5.4 mmol/L and/or 2-hour plasma glucose > 7.9 mmol/L Exclusion criteria: not stated.
Interventions	Intervention (n = 63): the intervention comprised instruction in a moderately energy restricted diabetic diet providing between 1590-1776 kcal (70% RDA) Control (n = 54): the control group were instructed in a diabetic diet which was not energy restricted, providing approximately 2010-2220 kcal a day

Outcomes	Weight gain, pre-eclampsias, induction of labour, caesarean delivery, shoulder dystocia, birthweight > 4000 g, birthweight > 90th centile, assisted delivery Weight gain was calculated as the difference between prepregnancy weight and delivery weight	
Notes	Age (intervention, control) 30.2, 30.6 years. Gestation at diagnosis(intervention, control) 28.1 ± 5.8, 28.3 ± 4.6 weeks BMI at diagnosis (intervention, control) 37.9 ± 0.7, 38.0 ± 0.7 kg/m²	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Low risk	Women were allocated at random using opaque numbered envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and the Diabetes Service staff were blinded to the allocation to diet group Medical staff were blinded to the group allocation of each participant
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up 6.4% (8), 4 for each group.
Selective reporting (reporting bias)	Unclear risk	Could not be determined.
Other bias	Low risk	The groups were similar in level of education, employment, racial distribution, and alcohol and cigarette consumption There were no significant differences at enrolment in weight, or energy expenditure

Rauh 2013

Methods	Cluster-RCT, open-label at 8 gynaecological practices in Germany from February 2010 to August 2012
Participants	General population. 250. Inclusion criteria: older than 18, 1 live fetus, < 18 weeks' gestation, BMI ≥ 18.5 kg/m ² ,

	and able to speak sufficient German Exclusion criteria: if they had any condition preventing physical activity, such as cervical incompetence, placenta praevia, or persistent bleeding. Prepregnancy diabetes or uncontrolled diseases that may affect weight development like thyroid dysfunction, or psychiatric diseases
Interventions	Intervention group: lifestyle counselling (n = 167) Intervention consisted of 2 individually delivered counselling sessions focusing on diet, physical activity and weight self-monitoring, delivered at the 20th (60 min) and 30th week (30 min) by trained researchers Control group: routine care (n = 83).
Outcomes	The primary outcome was the proportion of pregnant women exceeding weight gain recommendations of the IOM. The secondary outcome variables were maternal weight retention at 4 months postpartum and short-term obstetric and neonatal outcomes
Notes	Age (intervention, control): 32.2 [4.4]/30.8 [4.9]. Enrolment gestational age: 9 (8-11)/7 (6-8). Pregpregnancy BMI: 21.7 (19.9-23.7)/22.8 (20.6-26.6). We were unable to adjust reported data for clustering and baseline differences, therefore we did not pool these data The study report gave adjusted MD for GWG of -1.7 kg (-3.0 to -0.3) in favour of the intervention, and for excessive GWG an adjusted OR of 0.5 (0.3 to 0.9) Authors concluded that "Lifestyle counselling given to pregnant women reduced the proportion of pregnancies with excessive GWG without increasing suboptimal weight gain, and may exert favourable effects on postpartum weight retention"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer generated allocation table. "Gynaecological practices were randomised (rather than individuals)."
Allocation concealment (selection bias)	Low risk	"Randomisation was performed by a researcher not involved in the study design thereby preventing allocation bias."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not possible due to "the nature of the study".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding not possible for study staff due to "the nature of the study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No loss of clusters. 15/167 women in the intervention group and 9/83 control group women were lost to follow-up. Women in

Rauh 2013 (Continued)

		the intervention group dropped out for personal reasons (5), miscarriage or late-term abortion (3), complications of pregnancy (3) and preterm delivery (4). Control women dropped out because of personal reasons (1), moved away (1), unable to contact (2) and preterm delivery (5)
Selective reporting (reporting bias)	Unclear risk	Protocol not seen. Appropriate analysis methods used for clusters. Results were adjusted for age and prepregnancy BMI, which was higher in the control group. ITT not stated
Other bias	High risk	"During recruitment it turned out that it was easier to recruit women for the intervention group than for the control group, yielding a 2:1 ratio", instead of 1:1. Practices differed in size with 227 vs 129 women were eligible for the intervention and control groups, respectively Baseline characteristics differed significantly with regard to pregravid BMI ($P = 0.003$) and BMI at booking ($P = 0.008$), with a higher proportion of women in the control group considered obese or overweight (16.2% vs 31.4%; $P = 0.009$). Mean age was younger and gestational age at booking was significantly earlier in the intervention clusters. Although results were adjusted for BMI, age and clustering, there may also have been other (unknown) differences between the women in these groups Preterm birth and pregnancy complications NR as outcomes and these women were excluded from the analysis

Renault 2014

Methods	3-arm RCT at 1 hospital in Hvidovre in Denmark from March 2009 to March 2012
Participants	High risk. Obese. 425 randomised. 389 analysed. Inclusion criteria: pregnant women with a prepregnancy BMI of 30 kg/m² or greater. Age older than 18 years, a singleton pregnancy, and a normal scan in weeks 11-14, gestational age at inclusion of less than 16 weeks, and an ability to read and speak Danish Exclusion criteria: multiple pregnancy, pregestational diabetes, or other serious diseases limiting their level of physical activity, previous bariatric surgery, or alcohol or drug abuse

Interventions	Comparison of 3 groups. Intervention groups: intervention 1: physical activity and diet (n = 130); intervention 2: physical activity only (n = 125). The physical activity intervention included encouragement of increase physical activity, aiming at a daily step count of 11,000, monitored by pedometer assessment on 7 consecutive days, every 4 weeks. Dietary intervention included follow-up on a hypocaloric Mediterranean-style diet. Instruction was given by a dietician every 2 weeks with alternating outpatient visits and phone calls, including weight measurement, encouragement and correcting advice Control group: routine care (n = 134).
Outcomes	Primary outcome: GWG. Secondary outcomes: complications of pregnancy and delivery and neonatal outcome
Notes	Age (intervention 1, intervention 2, control): 31.2 [4.4]/ 30.9 [4.4]/31.3 [4.2] Enrolment gestational age was 11-14 weeks. Prepregnancy BMI: 34.4 [4.2]/34.1 [4.4]/33.7 [3.5]. GWG was calculated from the 36-37 week weight minus prepregnancy self-reported weight and was reported as median (range) so could not be included in the review meta-analysis for this outcome. GWG in the physical activity plus diet group was 8.6 kg (-9.6 to 34.1) vs 9.4 kg in the physical activity group (-4.4 to 28.2) vs 10.9 kg in the control group (-4.4 to 28.7) (P = 0.024). 1 woman in the physical activity group had a placental abruption and stillbirth Authors concluded that "No significant difference was found between the 2 intervention groups. Physical activity intervention assessed by pedometer with or without dietary follow-up reduced GWG compared with controls in obese pregnant women. The pedometer intervention is an inexpensive methods of increasing daily physical activity and can easily be implemented into daily clinical practice"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization was stratified according to parity to ensure equal distribution of primiparous in the 3 groups."
Allocation concealment (selection bias)	Low risk	"Web allocation by an independent organization properly concealed the procedure."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not possible due to the nature of the study.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding not described.

Renault 2014 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition rates for most outcomes. However, physical activity scores had > 20% missing data and we considered these data high risk
Selective reporting (reporting bias)	Unclear risk	Could not determine.
Other bias	Low risk	Baseline characteristics were comparable. Good compliance.

Rhodes 2010

Methods	RCT (pilot study), set in Beth Israel Deaconess Medical Center, Boston, MA, and Children's Hospital Boston, Boston, MA, USA	
Participants	Inclusion criteria: pregnant women with prepregnancy or 1st trimester BMI equal to or greater than 25 kg/m² and less than 45 kg/m², singleton pregnancy, willing to consume the diets for duration of pregnancy, participant to be at week 28 or less of pregnancy at baseline visit Exclusion criteria: smoking during pregnancy, major medical illness (e.g. diabetes mellitus, hypertension, thyroid disease), taking prescription medication known to affect body weight, alcohol consumption during pregnancy, intention to deliver infants in the environment outside of Beth Israel Deaconess Medical Center, Boston, high level of physical activity	
Interventions	Intervention group 1: nutrition education, dietary counselling, and a low-GI diet Intervention group 2: nutrition education, dietary counselling, and a low-fat diet	
Outcomes	Maternal outcome: weight change. Infant outcome: macrosomia, large-for-gestational age, caesarean delivery	
Notes	Age (intervention, control): 33.7 [3.9]/33.2 [3.7]. Enrolment gestational age: 19.8 (5)/19.6 (4.3). Prepregnancy BMI (intervention, control): 32.1(4.6)/ 31.2 (3.1)	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly "permuted blocks of 2 and 4 preventing anticipation of future assignments
Allocation concealment (selection bias)	Low risk	Separate random assignment envelopes for each stratum. Random assignment envelopes were prepared by the hospital clinical trials unit

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Formal blinding of participants was not possible, although participants were not informed of their group assignments. The following staff were blinded to group assignment: obstetricians who provided clinical care to women; nurses who measured maternal body weight and blood pressure, collected and processed maternal blood samples, and analysed urinalyses; labour and delivery room nurses who obtained birthweight; laboratory staff who analysed maternal blood; and staff who performed data entry
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Staff who performed maternal body composition analysis, 24-h dietary recalls, and infant anthropometric measurements “were predominantly, but not always”, blinded due to logistical considerations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	46 women were randomised and infant outcomes were available for 45. There was some loss to follow-up among women with outcome data at 36 weeks available for 38. Reasons for loss were explained and loss was reasonably balanced across groups. It was stated that analysis was by randomisation group irrespective of whether or not women received the intended intervention
Selective reporting (reporting bias)	Unclear risk	Assessment from published study report.
Other bias	Low risk	Baseline characteristics of participants did not differ between intervention groups

ROLO 2012

Methods	RCT conducted at a maternity hospital in Ireland with recruitment from January 2007 to January 2011
Participants	800 randomised, 759 analysed. Inclusion criteria: secundigravid women whose first baby was macrosomic (birthweight > 4.0 kg) Exclusion criteria: underlying medical disorders, previous history of gestational diabetes, those on any drugs, and those unable to give full informed consent, age less than 18 years, gestation greater than 18 weeks, and multiple pregnancy

Interventions	Low GI dietary intervention (n = 394) involving 1 dietary education session lasting 2 hours in groups of 2-6 women with a dietitian at baseline. Follow-up reinforcement sessions were held at 28 and 34 weeks' gestation. Women received written resources about low GI foods Control group: routine care (n = 406).
Outcomes	Primary outcome: birthweight. Secondary outcomes: GWG, maternal GI and dietary intake.
Notes	GTT was done at 28 weeks' gestation. Women completed food diaries. Other outcomes were recorded on delivery. Age (intervention, control): 32 [4.2]/32 [4.2] Enrolment gestational age: 13 [2.3]/12.9 [2.2]. Recruitment BMI: 26.8 [5.1]/26.8 [4.8]. Glucose challenge test at 28 weeks showed significantly less women in the intervention group vs control group with glucose intolerance defined as GCT > 7.8 mmol/L (54/350 [15%] vs 79/371 [21%])

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The research midwife did the randomisation by using computer generated allocations in a ratio of one to one."
Allocation concealment (selection bias)	Low risk	"sealed opaque envelopes."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition rates for most outcomes.
Selective reporting (reporting bias)	Unclear risk	Excluded women who did not receive allocated intervention (i.e. per protocol analysis)
Other bias	Low risk	Baseline characteristics were comparable. Good compliance.

Ronnberg 2014

Methods	Registered, open-label, parallel assignment RCT conducted in Sweden. ID NCT00451425
Participants	General population: 445 women randomised, 374 analysed. Included if > 18 years old, Swedish speaking, BMI $\geq$ 19, gestation < 16 weeks, and healthy Excluded if history of eating disorders or history of previous growth restricted child
Interventions	Intervention group: a motivational exercise intervention that included a personalised weight graph, GWG monitoring at each antenatal visit, and prescribed exercise to be at a "moderate level of exertion for approximately 30 min/day". The intervention was administered at routine antenatal visits by midwives. Control group: standard care. All women received basic dietary advice according to Swedish national guidelines
Outcomes	GWG (1990 IOM guidelines), weight retention up to 1ne year, fetal and maternal complications in pregnancy and during delivery, infant birthweight and infant weight up to 1 year of age
Notes	Age: 29.9 [4.5]/ 29.9 [4.8]. Enrolment gestational age: 10.7 vs 9.7 weeks. 72% normal weight women, 28% overweight or obese.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated in blocks of variable sizes between 4 and 8."
Allocation concealment (selection bias)	Low risk	"Sealed, opaque, sequentially numbered envelopes were kept by administrative personnel not related to the study." A research assistant opened the next envelope and informed the midwife telephonically of each group allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up was 8% in the intervention group and 11% in the control group. ITT analysis performed

Ronnberg 2014 (Continued)

Selective reporting (reporting bias)	Unclear risk	Only GWG outcomes reported. Other maternal and fetal outcomes were stated as having "no significant difference between groups". Unpublished data requested
Other bias	Unclear risk	Gestational age at recruitment was statistically significantly different (10.7 weeks vs 9.7 weeks, for intervention and control groups, respectively)

Ruchat 2012

Methods	RCT of 2 interventions compared with historical control in Canada	
Participants	General population, 73 recruited, 49 analysed. Inclusion criteria: normal weight women with singleton pregnancies between 16 and 20 weeks' gestation Exclusion criteria: specific exclusion criteria included the following: maternal age < 18 years or > 40 years, smoking, multiple pregnancy, presence of chronic disease, or other contraindications to exercise	
Interventions	2 lifestyle interventions vs an historical control. Intervention groups: interventions were moderate-intensity exercise plus diet (n = 26), vs low-intensity exercise plus diet (n = 23). The low-intensity exercise intervention consisted of a walking program that corresponded with 30% HRR (oxygen consumption reserve) whereas the moderate-intensity program corresponded with a 70% HRR. The exercise was performed 3 to 4 times per week, with 1 session per week supervised. Participants wore an HR monitor to ensure they were exercising within the predetermined target HR zone Control group: control group were 45 normal weight women with singleton pregnancies who did not participate in a structured exercise program All participants received a diet plan based on a modified diabetic diet	
Outcomes	GWG, maternal weight retention 2 months postpartum, infant birthweight	
Notes	We only included data from the randomised participants, i.e. the low intensity intervention vs moderate intensity intervention. As control group was not randomised, we did not use these data Age (intervention 1, intervention 2): 30.4 [4.5]/ 31 [3.8]. Enrolment gestational age: 17 [1.5]/17.5 [1.5]. Prepregnancy BMI: 21.7 [1.9]/22.1 [1.7]. Diet outcomes were collected between 34 and 36 weeks' gestation. Women were weighed weekly in the laboratory. Delivery and newborn data were obtained from medical records and complication during delivery were obtained from maternal recall within 6-18 hours after delivery Authors concluded that "Results suggest that a prenatal nutrition exercise program regardless of exercise intensity, reduced excessive GWG and decreased weight retention at 2 months postpartum in women of normal weight before pregnancy"	

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"All the participants were randomised using a block procedure with four subjects per block."
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding not described. Exercise and diet logs were recorded by the participants at home
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 49 participants (67%) out of 73 completed the study. Even if 1 excludes the 7 women who "decided to withdraw after the peak exercise test" (before randomisation), withdrawal is still > 20%. Similar numbers withdrawn from both groups
Selective reporting (reporting bias)	Unclear risk	Could not determine.
Other bias	High risk	Control group was historical, not randomised; therefore, these data were not used in the review. See Potential biases in the review process .

Ruiz 2013

Methods	RCT at 3 primary care hospitals in Madrid, Spain, from September 2007-January 2011
Participants	General population, 962 randomised and analysed. Inclusion criteria: women who were sedentary (not exercising for > 20 mins on > 3 days a week), with singleton and uncomplicated gestations, not at high risk of preterm delivery (i.e., previous preterm birth) and not participating in any other trial were able to participate in this study Exclusion criteria: women with any obstetric contraindication to exercise were not eligible to participate
Interventions	Intervention group: exercise intervention (n = 481). The intervention included light- to moderate-intensity aerobic and resistance exercises performed 3 days a week (50-55 mins per session) from 9 weeks to weeks 38-39. Exercise sessions included 8-10 participants Control group: routine care (n = 481).

Outcomes	Primary outcome: GWG. Secondary outcomes: Maternal and fetal outcomes, including birthweight, gestational age, type of delivery (caesarean, etc), Apgar scores, childbirth, gestational diabetes and hypertension	
Notes	Age (intervention, control): 31.6 [4]/ 31.9 [4]. Enrolment gestational age was 5-6 weeks. Pregpregnancy BMI: 23.7 [3.9]/23.5 [4.2]. GWG was calculated from measured weight at last visit minus weight at first prenatal visit. Other outcomes were obtained from hospital records after delivery Authors concluded that "Supervised exercise of light to moderate intensity can be used to prevent excessive gestational weight gain, especially in normal weight women. The effects seemed to be more pronounced in normal weight women..."	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer generated."
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	14% attrition overall. 68 women in the control arm were lost to follow-up because of threat of premature delivery (n = 11), persistent bleeding (n = 9), a move to another hospital (n = 20), or miscellaneous personal reasons (n = 28). 70 women in the intervention arm were lost to follow-up due to threat of premature delivery (n = 14), persistent bleeding (n = 7), a move to another hospital (n = 25), or miscellaneous personal reasons (n = 24). No protocol deviations
Selective reporting (reporting bias)	Low risk	Expected outcomes reported.
Other bias	Low risk	None noted. Baseline characteristics were comparable.

Santos 2005

Methods	Randomised clinical trial, set in a referral centre prenatal clinic in Porto Alegre, Brazil, during the period 2000-2002
Participants	Inclusion criteria: healthy, nonsmoking pregnant women, aged 20 years or more, of gestational age less than 20 weeks, having a BMI between 26 and 31 kg/m ² (corresponding to a prepregnancy BMI of 25-30 kg/m ²) (overweight), and without diabetes or hypertension Exclusion criteria: not stated.
Interventions	Intervention (n = 37): the intervention consisted of a program of supervised physical exercise of 60 mins duration, performed 3 times per week for 12 weeks. Each session consisted of 5-10 mins of warm up, 30 mins of heart rate-monitored aerobic activity, 10-15 mins of exercise involving upper and lower limbs, and 10 mins of stretching and relaxation. Aerobic activities were always performed between 50% and 60% of the maximum predicted heart rate, never exceeding 140 beats per min. The exercises followed the recommendations concerning physical activity practice during pregnancy according to the American College of Sports Medicine, and the ACOG Control (n = 35): the control group participated in once-weekly sessions that included relaxation (respiratory exercises and light stretching but no aerobic or weight-resistance exercises) and focus group discussions concerning maternity. Control participants were neither encouraged to exercise nor discouraged from exercising
Outcomes	Weight gain, low birthweight, prematurity. Weight gain was calculated from difference between weight at baseline and weight after 12 weeks of intervention
Notes	At baseline; age (exercise, control) 26.0 ± 3.4, 28.6 ± 5.9 years BMI (exercise, control) 28.0 ± 2.1, 27.5 ± 2.1 kg/m ² . Gestational age (exercise, control) 17.5 ± 3.3, 18.4 ± 3.9 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Women were randomised following a blocked sequence generated from a random number table by a statistician not participating in other aspects of the study
Allocation concealment (selection bias)	Low risk	The study co-ordinator implemented the randomisation by using numbered, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded.
Blinding of outcome assessment (detection bias)	Low risk	The same cardiologist, blinded to treatment allocation, performed both tests

All outcomes		The anaerobic threshold was determined by review of the gas exchange curves by 2 cardiologists working independently and blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow-up 22%, 19.6%, and 23.9% in intervention and control groups.
Selective reporting (reporting bias)	Unclear risk	Could not determine.
Other bias	High risk	Women in the intervention group were somewhat younger, had higher physical activity, and were earlier in their pregnancy

Stafne 2012

Methods	RCT conducted at St Olavs Hospital, Trondheim University Hospital, and Stavanger University Hospital in Norway with recruitment from April 2007 to June 2009	
Participants	855 randomised, 702 analysed. Inclusion criteria: white women aged 18 years or older with a singleton live fetus Exclusion criteria: high-risk pregnancies or diseases that could interfere with participation (or both). For practical reasons, women who lived too far from the hospitals to attend weekly training groups (more than 30-min drive) were excluded	
Interventions	Intervention group: 12 weeks regular standardised exercise program including aerobic activity, strength training, and balance exercises. The exercise program followed standard recommendations and included moderate-intensity to high-intensity activity 3 or more days per week. Physiotherapist-supervised training sessions of 60 mins in groups of 8-15 women were offered once per week Control group: routine care (women were not discouraged from exercising)	
Outcomes	Primary outcome: GDM, insulin resistance. Secondary outcomes: maternal weight, BMI, newborn weight, gestational age, Apgar score	
Notes	Baseline assessment at 18-22 weeks, outcomes assessed at 32 to 36 weeks' gestation Age (intervention, control): 30.5 [4.4]/ 30.4 [4.3]. Enrolment gestational age was 18-22 weeks. Recruitment BMI: 24.7 [3]/25 [3.4].	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Concealed randomization in blocks of 30 was performed at the Unit for Applied

Stafne 2012 (Continued)

		Clinical Research, by a Web-based computerized procedure.“
Allocation concealment (selection bias)	Low risk	”concealed randomisation.“
Blinding of participants and personnel (performance bias) All outcomes	High risk	”Because of the nature of the study it was not blinded.“
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessment of primary outcome (insulin resistance) ”was blinded for group allocation“
Incomplete outcome data (attrition bias) All outcomes	High risk	18% dropout overall with more dropouts in the control group (24% vs the intervention group 13%)
Selective reporting (reporting bias)	Unclear risk	Could not determine. ITT performed.
Other bias	Low risk	None noted. Baseline characteristics similar.

Szmeja 2011

Methods	RCT conducted in Adelaide, Australia. Study period not stated
Participants	High risk. 193 women included. Inclusion criteria: women with a BMI ≥ 25 kg/m ² and a live singleton pregnancy between 10 and 20 weeks’ gestation Exclusion criteria not stated.
Interventions	Intervention group (98 women): received an ”informational DVD“ Control group (95 women): ”No DVD“.
Outcomes	Self-reported knowledge of health dietary and lifestyle choices, satisfaction with pregnancy care
Notes	No statistically significant differences reported. Authors concluded that the intervention was not effective

Risk of bias

Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Appear to be self-reported outcomes only.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to make a judgement.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make a judgement.
Other bias	Unclear risk	This report has not been published in full, possibly because the intervention was not effective

Thornton 2009

Methods	RCT, set in the ambulatory obstetric clinics of 3 tertiary care medical centres - Morristown Memorial Hospital, St Luke's-Roosevelt Hospital Center, and Jamaica Hospital Medical Center. Each study site was an urban, public clinic of a teaching hospital, New York Medical College
Participants	Inclusion criteria: pregnant with a single fetus between 12 and 28 weeks of gestation that had a BMI greater than or equal to 30 kg/m ² Exclusion criteria: women with pre-existing diabetes, hypertension, or chronic renal disease
Interventions	Intervention (n = 116): monitored group; counselled in nutrition by a registered dietitian and given a more detailed dietary intake protocol. The nutrition program for the monitored women followed dietary guidelines similar to those used in women with the diagnosis of gestational diabetes. The women in this group were asked to record in a diary all of the foods and beverages eaten during each day Control (n = 116): unmonitored group; counselled in nutrition by a registered dietitian regarding conventional prenatal nutrition guidelines
Outcomes	Weight gain, weight retention (calculated from the difference between weight at 6 weeks' postpartum and weight at baseline) GDM, pre-eclampsia, gestational hypertension, haemorrhage/infection postpartum, preterm delivery (< 37 weeks), labour induction, caesarean delivery, macrosomal infant (> 4500 g) Weight gain was weight difference between the baseline(12-28 weeks) pregnancy weight and weight before delivery
Notes	Age (intervention, control) 26.8, 27.3. BMI (intervention, control) 37.41 ± 7.01, 38.22 ± 7.48 kg/m ²

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A random-number table was used to assign each consecutively numbered envelope to either the study or control group in blocks of 10
Allocation concealment (selection bias)	Low risk	Envelopes were prepared and sequentially numbered. A card indicating the assigned group was placed in the envelope, and the envelope was sealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The ITT principle was performed. Loss to follow-up 9.7%.
Selective reporting (reporting bias)	Unclear risk	Could not determine.
Other bias	Low risk	Demographic data for the randomised groups were comparable.

Vesco 2013

Methods	Parallel-arm RCT conducted by Harvard Medical School, USA.
Participants	160 planned, 114 randomised so far. Inclusion criteria: women aged 18 or older, who were obese at the beginning of pregnancy (BMI ≥ 30 kg/m ²); 10-20 weeks' gestation Exclusion criteria: gestational age > 20 weeks, multifetal pregnancy, anticipated disenrolment prior to delivery, non-English speaking, plans to move within the year, type 1 or 2 diabetes mellitus (or gestational diabetes), and other medical conditions that require specialised nutritional care (e.g. history of bariatric surgery) or conditions that may affect weight gain (e.g. severe hyperemesis gravidarum)
Interventions	Intervention group: lifestyle intervention (diet plus exercise) (n = 56). Following randomisation, all participants receive a 45-min dietary consultation. They were encouraged to follow the Dietary Approaches to Stop Hypertension diet (DASH) without sodium restriction and received an individualised calorie intake goal, a second individual counselling session and attend weekly group meetings (90 min) with weigh-ins, food and

	activity logs until they give birth. Women are encouraged to accumulate at least 30 min of moderate intensity activity per day. Pedometers recorded steps with at target of 10, 000 steps daily and were only provided to the intervention group Control group: usual care (n = 58) with a 1-time advice session about healthy eating	
Outcomes	Primary outcomes: GWG, excessive weight gain, postpartum weight retention at 1 year (mean difference between postpartum and baseline weight), proportion of LGA neonates Secondary outcomes: feasibility and acceptability of the intervention, maternal dietary intake and physical activity, and infant birthweight, feeding patterns, and growth during the first year of life	
Notes	Median age (intervention, control): 29 (27-32), 29 (26-31). Mean BMI 36.7 (5.2) / 36.8 (4.7). 21% of sample had BMI > 40 kg/m ² . Data collection at 34-weeks' gestation and at 2-weeks' and 1-year postpartum Enrolment at 10-20 weeks' gestation.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation ...using a computerised algorithm to generate the random assignments in blocks of four."
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Good follow-up achieved.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported. ITT analysis.
Other bias	Unclear risk	Follow-up weight gain data were collected at 34 weeks (i.e. earlier than most other included studies)

Vinter 2012

Methods	RCT conducted at 2 university hospitals in Odense, Denmark from October 2007 to October 2010
Participants	360 randomised, 304 analysed. Included obese women aged 18-40 years, 10-14 weeks' gestation, BMI of 30-45kg/m ² Excluded if chronic medical conditions, prior serious obstetric complications, alcohol/drug abuse, non-Danish speaking, multiple pregnancy, positive GTT
Interventions	Intervention group: a lifestyle intervention consisting of dietary counselling and exercise (n = 180). The intervention involved dietary advice on 4 occasions (15, 20, 28 and 35 weeks) by a dietician. Energy requirements were personalised for each participant. Exercise intervention included a pedometer, free gym membership for 6 months, encouraged to do 30-60 min moderate physical activity daily. At the gym they had closed training classes with a physiotherapist for 1 hour each week Control group: routine care (n = 180).
Outcomes	GWG, pre-eclampsia, hypertension, GDM, caesarean section, macrosomia, LGA, admission to NICU, maternal weight retention at 6 months postpartum, infant and childhood weight
Notes	GWG was defined as weight gain at 35 weeks. Obstetric and neonatal outcomes were obtained from medical records. Childhood weight not yet reported Age (intervention, control): 29 (27-32)/29 (26-31). Enrolment gestational age was 10-14 weeks. Recruitment BMI: 33.4 (31.7-36.5)/33.3 (31.7-36.9).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated numbers" 1:1, stratified for smoking.
Allocation concealment (selection bias)	Low risk	"sealed envelopes."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	56/360 (15%) dropped out for primary outcomes. Similar between groups
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.

Other bias	Low risk	None noted. Baseline characteristics comparable.

Vitolo 2011

Methods	RCT (pilot study), set in primary care settings in Porto Alegre, Brazil
Participants	Inclusion criteria: gestational age between 10 and 29 weeks; women attending the pre-natal care unit of the health unit Exclusion criteria: positive testing for HIV, previous diagnostic of diabetes, hypertension, anaemia or another condition that needed a special diet and age over 35 years
Interventions	Intervention group: (159 women) weight and diet were assessed at recruitment. The aim of the intervention was to improve diet and encourage weight-appropriate weight gain in pregnancy. For low weight women, the priority was increasing the energetic density of the meals. For normal weight women, daily consumption of vegetables, greens, fruit and water were encouraged and women were advised to restrict consume of fat-rich foods and oil in cooking. For the overweight women, the intervals between meals were prioritised and women were encouraged to restrict their consumption of snacks. Women received a further interview 1 month later to reinforce messages Control group: (162 women) women did not receive any special intervention but were informed about their weight and nutritional status and advised to seek professional help if they were under or overweight. Their doctors were also provided with the results of the nutritional evaluation
Outcomes	Weight gain.
Notes	Reported average weekly weight gain which was significantly lower in the overweight women in the intervention group than the control group (342.2 g [143.6] vs 420 g [185.4]; P = 0.01)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Women were randomised by means of a dark pouch with 2 equal sized cubes containing the term intervention in 1 and control in the other
Allocation concealment (selection bias)	Unclear risk	2 cubes were concealed in a dark pouch and 1 was removed at the point of randomisation which indicated allocation. (It is possible that this could be changed by the person carrying out randomisation.)

Vitolo 2011 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	315 women accepted participation in the study. There were 307 women with anthropometric data collected in the last trimester
Selective reporting (reporting bias)	Unclear risk	The results relate to the number of women with excessive or low weight gain at different gestational ages
Other bias	Unclear risk	'Risk of bias' assessment from translated notes.

Wilkinson 2012

Methods	RCT conducted at a maternity hospital in Australia with recruitment from August 2010 to March 2011
Participants	Randomised 360, analysed 242. Included if attending their booking visit at the MH research site and were 18 years or older (or under 18 years, with the consent of a parent or guardian) Excluded if unable to read and speak English at a level that allowed completion of pen-and-paper surveys
Interventions	Intervention group: a lifestyle intervention (diet plus exercise, smoking cessation, etc) (n = 178) consisting of a 1-hour 'Healthy start to pregnancy' workshop with a 12 page booklet with evidence based information, with goal setting and self-monitoring activities Control group: routine care (n = 182).
Outcomes	Good nutrition, PA, GWG awareness, number of cigarettes smoked, BMI
Notes	Outcomes assessed at recruitment and 12 weeks later at around 26 weeks Age (intervention, control): 29.5 [5.1]/29 [4.7]. Enrolment gestational age: 14.5 [3]/14.2 [3]. Prepregnancy BMI: 25.4 [5.2]/24.6 [5.5]. ITT analysis showed increased weekly activity scores in mins in the intervention group. Only per protocol analyses showed significant differences in diet quality and mean servings of vegetables and fruit in the intervention group at the follow-up interview (26 weeks)
<i>Risk of bias</i>	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computerized randomisation process."
Allocation concealment (selection bias)	Low risk	"allocation was concealed using sealed opaque envelopes."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not described. Most outcomes, including activity scores and food consumption were self-reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Only half the women attended the workshop, and overall response at the second assessment was 67%
Selective reporting (reporting bias)	Unclear risk	Could not determine. Reported ITT and per protocol analyses. Few review outcomes reported. Little usable data
Other bias	Low risk	Baseline characteristics overall were comparable.

Wolff 2008

Methods	RCT, set in Copenhagen, Denmark.
Participants	Inclusion criteria: pregnant obese women (BMI > 30 kg/m ²), nondiabetic non-smoking and Caucasian recruited at 15 ± 3 weeks of gestation. Exclusion criteria: smoking, age < 18 or > 45, multiple pregnancy, or medical complication
Interventions	Intervention (n = 23): restriction of GWG to 6-7 kg by 10 consultation of 1 hour each with trained dietitian. The women were instructed to eat a healthy diet according to the official Danish dietary recommendations (% fat, protein, CHO, 30, 15-20, 50%-55%) . The energy intake was restricted based on individually estimated energy requirements and estimated energetic cost of fetal growth Control (n = 27): the control group had no consultations with the dietitian and had no restrictions on energy intake or GWG All participants followed the routine clinical schedule.
Outcomes	Weight gain, weight retention at 4 weeks' postpartum, pre-eclampsias, caesarean delivery Weight gain was calculated as difference between self-reported prepregnancy weight and weight just before delivery

Notes	Age (intervention, control) 28 ± 4, 30 ± 5 years. Gestational age (intervention, control) 15 ± 2, 16 ± 3 weeks BMI at inclusion visit (intervention, control) 34.9 ± 4, 34.6 ± 3 kg/m²	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The computerised randomisation took place after the women had given written informed consent
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The physicians and midwives were blinded in regard to the treatment assignment, and women were asked not to reveal their allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow-up 24%: 17.8% in intervention group, 28.9% in control group
Selective reporting (reporting bias)	Unclear risk	Could not determine.
Other bias	Low risk	Baseline characteristics were similar.

ACOG: the American Congress of Obstetricians and Gynecologists

ANC: antenatal clinic

BMI: body mass index

BP: blood pressure

CHO: carbohydrate

GDM: gestational diabetes mellitus

GI: glycaemic index

GWG: gestational weight gain

HbA1C: haemoglobin A1C

HGI: high glycaemic index

Hi-Lo: high-low exercise

IOM: Institute of Medicine

ITT: intention-to-treat

LGA: large-for-gestational age

LGI: low glycaemic index

Lo-Hi: low-high exercise

min: minutes

Mo-Mo: moderate-moderate exercise

n: number

NICU: neonatal intensive care unit
 NR: not reported
 OGTT: oral glucose tolerance test
 QoL: quality of life
 RCT: randomised controlled trial
 RDA: recommended dietary allowance
 SD: standard deviation
 SGA: small-for-gestational age
 VLDL: very low-density lipoprotein
 vs: versus

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Asemi 2011	RCT of effect of probiotic yogurt during pregnancy on inflammatory factors, lipid profiles, oxidative stress and insulin resistance, not on preventing excessive weight gain
Bechtel-Blackwell 2002	Quasi-RCT.
Boileau 1968	Irrelevant intervention.
Breslow 1963	Non-RCT.
Campbell 2004	Participants included pregnant and nonpregnant women.
Daley 2014	Abstract of the process evaluation of an RCT.
Davenport 2011	Quasi-RCT of a target weight program intervention in pregnancy
Faucher 2008	It was not clear that women in this study were pregnant (community weight loss intervention)
Graham 2014	Formative research for e-Mons study not RCT results.
Gray-Donald 2000	Non-RCT.
Hauner 2012	RCT omega-3 fatty acids on infant adipose tissue, not an intervention to reduce excessive weight gain in pregnancy
Hausenblas 2008	Participants included both pregnant and postpartum women.
Ismail 1990	Not a relevant intervention. This study examined the use of cefoxitin (an antibiotic) for the prevention of post-caesarean-section infection
Kinnunen 2007	Non-RCT.
Lindsay 2014	Abstract of RCT (probiotics) without gestational weight gain outcomes

(Continued)

Maitland 2014	Abstract of a pilot cross-over study of only 16 women to evaluate a dietary supplement
Mohebi 2009	Quasi-RCT protocol.
Moses 2006	Quasi-RCT.
Mottola 2010	Not a RCT.
Olson 2004	Non-RCT.
Silverman 1971	Irrelevant intervention.
Stutzman 2010	Quasi-RCT on the effect of exercise on blood pressure and heart rate variability, not excessive weight gain
Te Morenga 2011	This study did not include pregnant women.
Walker 1966	Non-RCT.
Wisner 2006	Participants were postpartum women.

RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Shakeri 2012

Methods	This study requires translation from Farsi before it can be classified
Participants	
Interventions	
Outcomes	
Notes	

Characteristics of ongoing studies *[ordered by study ID]*

Astrup 2013

Trial name or title	An optimised programming of healthy children (APPROACH).
Methods	RCT, single blind, parallel assignment. Location: Denmark.
Participants	390 obese pregnant women.
Interventions	High-protein/low-GL diet vs low-protein/high-GL diet.
Outcomes	Primary: GWG. changes in bodyweight, body composition, body fat Secondary: growth and development of fetus.
Starting date	01/11/2013.
Contact information	Nina RW Geiker, nina.rica.wium.geiker@regionh.dk, Copenhagen University Hospital at Herlev
Notes	Estimated completion date: December 2015 (final data collection date for primary outcome measure)

Atkinson 2013

Trial name or title	Be healthy in pregnancy (B-HIP): an RCT to study nutrition and exercise approaches for healthy (BHIP)
Methods	RCT, 2-arm randomised 1-site trial, parallel assignment, single blind Location: Canada.
Participants	110 women with singleton pregnancies. Excluded: currently breastfeeding previous child, pregnancy resulting from in vitro fertilisation, and others
Interventions	Nutrition (energy high protein, low fat diet) and exercise (aerobic) vs standard prenatal care
Outcomes	GWG within IOM guidelines, maternal and infant outcomes.
Starting date	01/07/2012.
Contact information	Stephanie A Atkinson, PhD, satkins@mcmaster.ca, McMaster University
Notes	Estimated completion date: November 2016 (final data collection date for primary outcome measure)

Barakat 2012

Trial name or title	Effect of a supervised exercise program in obese and overweight pregnant women on outcomes and level of depression
Methods	RCT. Location: Spain.

Barakat 2012 (Continued)

Participants	150 obese and overweight pregnant women. Inclusion criteria · Being healthy and able to exercise following American College of Obstetricians and Gynecologists (ACOG) guidelines · Being able to communicate in Spanish. · Giving birth at Hospital Universitario de Fuenlabrada. · Having a BMI greater than 24.9. Exclusion criteria · Multiparity. · Obstetrician complications. · Being interested in the study after 18 weeks. · Not being regular in physical exercise program (minimum adherence 80%) · Younger than 18 years old.
Interventions	Behavioural: exercise group. Supervised physical conditioning program of 3, 55-60 minute sessions per week during whole pregnancy (from week 9 to 38). Each session consists of 25-30 minutes of cardiovascular exercise, 10 minutes of specific exercises (strength and balance exercises), and 10 minutes of pelvic floor muscles training. Aerobic activity was prescribed at light-to-moderate intensity, aiming for 55-60 of maximal heart rate. All women wore a heart rate (HR) monitor (Polar FT7) during the training sessions to ensure that exercise intensity was light-to-moderate
Outcomes	Primary outcomes: change from level of depression at the end of the pregnancy [Time frame: Up to 36 weeks] The Center for Epidemiological Studies-Depression scale (CES-D) was administered to all obese and overweight pregnant women at the beginning and at the end of their pregnancies Secondary outcomes · Maternal GWG [Time frame: 40-42 weeks]. · Maternal outcomes [Time frame: after labour]. · Fetal weight [Time frame: after labour].
Starting date	October 2009.
Contact information	Ruben Barakat, PhD, barakatruben@gmail.com , Universidad Politécnica de Madrid, Spain.
Notes	Final data collection date for primary outcome measure, January 2013

Brownfoot 2011

Trial name or title	Weighing in pregnancy.
Methods	RCT.
Participants	Pregnant women attending for antenatal care at < 20 weeks' gestation 18-45 years. Excluded multiple gestation or medical or psychiatric illness. (Target sample size 650.)
Interventions	Weighing as part of each antenatal visit compared with routine care

Brownfoot 2011 (Continued)

Outcomes	Weight gain within IOM and WHO recommendations; medical complications of pregnancy (pre-eclampsia, hypertension, gestational diabetes); need for induction of labour; mode of delivery; postpartum complication; infant birthweight; macrosomia and complications relating to macrosomia
Starting date	1st January 2010.
Contact information	fiona.brownfoot@thewomens.org.au
Notes	Emailed 22/9/14.

Callaway 2012

Trial name or title	Probiotics for the prevention of gestational diabetes in overweight and obese women
Methods	RCT, placebo, parallel, blinded. Location: Australia.
Participants	640 obese and overweight women. 18 to 50 years. Excluded: gestation > 16 weeks, pre-existing diabetes, pre-existing impaired fasting glucose or impaired glucose tolerance, GDM on early screening, and others
Interventions	Diet (administration of probiotics) vs placebo.
Outcomes	Gestational diabetes. GWG. pre-eclampsia, induction of labour, caesarean section. neonatal outcomes, biochemical and other outcomes
Starting date	01/06/2012.
Contact information	Prof Leonie Callaway, l.callaway@uq.edu.au, Royal Brisbane and Women's Hospital
Notes	

Chasan-Taber 2009

Trial name or title	A RCT of prenatal physical activity to prevent gestational diabetes: design and methods
Methods	RCT. A blocked randomisation is used such that both treatment groups are assigned an equal number of times in each set of 4 sequentially enrolled women
Participants	Location: Bay State Medical Center in western Massachusetts. Target number of participants: 364. Inclusion criteria: women are sedentary, with a diagnosis of GDM in a prior pregnancy defined according to American Diabetes Association (ADA) criteria Exclusion criteria: age < 18 or > 40 years, history of diagnosis of diabetes outside of pregnancy, hypertension, heart disease or chronic renal disease, current medications that adversely influence glucose tolerance, > 16 weeks' gestation, contraindications to participating in moderate-physical activity, inability to read English

Chasan-Taber 2009 (Continued)

	at a 6th grade level, self-reported participation in > 30 minutes of moderate-intensity or vigorous-intensity exercise on > 3 days/week, and non singleton pregnancy
Interventions	Exercise intervention: person education on exercise followed by weekly, biweekly and monthly mail and telephone follow-up Health and wellness intervention: person education health and wellness followed by weekly and monthly mail and telephone follow-up
Outcomes	Maternal weight gain (change in weight from pregravid to delivery), birthweight, Apgar score, caesarean delivery, macrosomia (> 4000 g) and LGA, defined as newborn weight the 90th percentile for completed gestational weeks using cutoff points defined by Oken
Starting date	April 2010.
Contact information	Lisa Chasan-Taber; lct@schoolph.umass.edu Megan Ward Harvey, meward@schoolph.umass.edu
Notes	1 paper has been published (Hawkins 2014). It found that the exercise arm had significantly greater increases in sports or exercise activity. Findings on GWG and neonatal outcomes are pending

Chasan-Taber 2013

Trial name or title	Lifestyle intervention in overweight and obese pregnant Hispanic women
Methods	RCT, parallel, double blind. Location: USA.
Participants	Estimated enrolment 333. Overweight or obese Hispanic women 16-45 years old. Excluded if type 2 diabetes, heart disease, or chronic renal disease. multi-gestational, and other exclusions
Interventions	PA and diet intervention materials and health education vs standard prenatal care
Outcomes	Insulin resistance, GWG, postpartum weight loss, postpartum cardiovascular risk and others
Starting date	01/01/2014.
Contact information	Lisa Chasan-Taber, ScD, lct@schoolph.umass.edu, University of Massachusetts, Amherst
Notes	Estimated completion date: 01/12/2018.

Choi 2011

Trial name or title	A pilot study of a mobile phone-based physical activity program in pregnant women
Methods	RCT, parallel, single blind. Location: USA.
Participants	30 physically inactive women at 10 - 20 weeks' gestation with pre-pregnancy BMI $\geq$ 18.5 Excluded if known medical or obstetric complication that restricts physical activity. History of eating disorders
Interventions	Study mobile phone app and activity monitor vs activity monitor
Outcomes	Physical activity, measured steps.
Starting date	01/10/2012.
Contact information	JiWon Choi, PhD, no email given, University of California, San Francisco
Notes	Estimated completion date: May 2014.

Downs 2011

Trial name or title	Determinants and outcomes of physical activity in pregnancy: findings from active MOMS, a randomised physical activity intervention for pregnant women
Methods	RCT.
Participants	Pregnant women (inclusion and exclusion criteria not described)
Interventions	2 physical activity interventions and a control group. 1 group received a structured intervention with face-to-face physical activity education, motivational support and moderate-physical activity on 2 days per week for 70 mins with an instructor. The 2nd group (lifestyle support) received educational support via mailed materials and phone support. The control group received standard care
Outcomes	Performance (physical activity).
Starting date	
Contact information	Danielle S Downs, The Pennsylvania State University, University Park, PA, USA
Notes	Study reported in brief abstract with preliminary findings.

Farajzadegan 2013

Trial name or title	Maternal-centred life-style modification program for weight gain management during pregnancy
Methods	RCT. Location: Iran.

Farajzadegan 2013 (*Continued*)

Participants	160 pregnant women between 6 to 10 weeks' gestational age who have no condition that requires medical care nor drug taking
Interventions	Nutrition and exercise (educational package, prenatal care log book and 10, 20-minute counselling sessions) vs standard prenatal care
Outcomes	GWG, BMI.
Starting date	Not stated.
Contact information	Dr Zahra Amini Pozveh, aminizahra2005@yahoo.com, Isfahan University of Medical Sciences
Notes	

Fernandez 2011

Trial name or title	Electronically-mediated weight interventions for pregnant and postpartum women
Methods	RCT, 3-armed, parallel, double blind. Location: USA.
Participants	Estimated enrolment 1641 pregnant women at or before 20 weeks' gestation Excluded BMI < 18.5 and > 35, multiple gestation, any previous conditions that could interfere with weight loss
Interventions	Behavioural intervention through a website during pregnancy and until 18 months postpartum or intervention through website during pregnancy only vs non weight-related content
Outcomes	GWG, postpartum weight retention, caloric intake, PA.
Starting date	01/05/2011.
Contact information	Diana Fernandez, no email given, University of Rochester.
Notes	Estimated completion date December 2014.

Ferrara 2014

Trial name or title	A pragmatic cluster randomised clinical trial of diabetes prevention strategies for women with gestational diabetes: design and rationale of the Gestational Diabetes' Effects on Moms (GEM) study
Methods	Cluster-RCT, multicentre, blinded. Location: USA.
Participants	2,320 women with a GDM diagnosis between March 27, 2011 and March 30, 2012 Excluded: neonatal loss, no telephone contact.

Ferrara 2014 (Continued)

Interventions	Nutrition and exercise (diabetes prevention program-derived print/telephone lifestyle intervention of 13 telephonic sessions) vs usual care
Outcomes	Proportion of women who reach a postpartum weight goal and total weight change. Postpartum glycaemia, blood pressure, depression, percent of calories from fat total caloric intake and physical activity levels
Starting date	March 27, 2011.
Contact information	Assiamira Ferrara, Assiamira.Ferrara@kp.org, Kaiser Permanente Northern California
Notes	

Goldberg 2012

Trial name or title	Randomised control pilot of a behaviour-based exercise and diet intervention to reduce risk factors for gestational diabetes among otherwise healthy pregnant women
Methods	RCT, parallel, open label. Location: USA.
Participants	30 healthy first trimester pregnant women 18 to 40 years. Excluded: hypertension, diabetes, known cardiopulmonary disease; orthopaedic problems or other conditions that would prevent regular physical activity
Interventions	Nutrition and exercise (20 interactive weekly sessions to promote daily exercise, vegetable and fruit intake, maintain a diet that is relatively lower in fat and rich in whole grains) vs standard medical care
Outcomes	Achieving 30 minutes of daily exercise, 4 or more times each week. Eating 5 or more servings of vegetables and/or fruits each day, pregnancy weight gain, fasting glucose, HbA1C, pregnancy weight gain, blood pressure, lipid and lipoprotein levels, pedometer records and more
Starting date	01/11/2012.
Contact information	Linn Goldberg MD, goldberl@ohsu.edu, Oregon Health and Science University
Notes	

Graziano 2013

Trial name or title	WATE study - gestational weight gain and the electronic medical record
Methods	RCT, parallel, open label. Location: USA.
Participants	Estimated enrolment 300. Pregnant women with a single intrauterine gestation. Excluded multiple gestation pregnancy.

Graziano 2013 (Continued)

Interventions	Weight alerts (electronic medical record popup/highlight in their chart, displaying the weight gain, patient perception, recommended guidelines for weight gain in pregnancy) vs usual display, with no flag nor highlight
Outcomes	Weight gain, primary outcome will be measured as the percent of patients who achieve their recommended weight gain goal in pregnancy
Starting date	01/10/2013.
Contact information	Scott Graziano, MD MS, sgrazia@lumc.edu, Loyola University.
Notes	Estimated primary completion date: October 2014 (final data collection date for primary outcome measure)

Hivert 2012

Trial name or title	Intervention to promote changes of healthy lifestyle (physical activity and nutrition) during gestation
Methods	RCT, parallel, open label. Location: Canada.
Participants	Estimated enrolment of 50 overweight or obese pregnant women at risk of developing diabetes mellitus Excluded if pre-pregnancy diabetes detected in the first trimester, multiple gestation, taking medications that can affect blood sugar or weight
Interventions	Healthy lifestyle counselling and PA sessions once a week until week 36 of gestation vs information about the recommended weight gain during pregnancy and an evaluation about of their nutritional and PA habits
Outcomes	Weight change during pregnancy, levels of maternal and fetal adipokines, maternal and fetal glycaemic control, healthy lifestyle and others
Starting date	01/12/2011.
Contact information	Marie-France Hivert, marie-france.hivert@usherbrooke.ca, Universitaire de Sherbrooke
Notes	Estimated completion date: January 2014. Emailed 25/9/14. Unpublished pilot study data for 20 women. was received on the 17/11/14

John 2014

Trial name or title	Healthy eating and lifestyle in pregnancy (HELP): a protocol for a cluster-randomised trial to evaluate the effectiveness of a weight management intervention in pregnancy
Methods	Cluster-RCT, blinded. Location: UK.
Participants	Target recruitment of 570 pregnant women aged 18 years or over, with a BMI ≥ 30 (kg/m ²) and between 12 and 20 weeks' gestation Excluded if unable to understand English, any pregnancy-related complications, any previous medical com-

John 2014 (Continued)

	plications, any nutritional complications, involved in other research
Interventions	Nutrition and exercise (weekly 1.5-hour weight management group) vs usual care and 2 leaflets giving advice on diet and physical activity
Outcomes	BMI at 12 months postpartum, GWG, QoL, mental health, waist-hip ratio, child weight centile, admission to neonatal unit, diet, and others
Starting date	Not stated.
Contact information	Elinor John, simpsonsa@cf.ac.uk, Cardiff University.
Notes	

King 2013

Trial name or title	Postprandial response to almond consumption in overweight Hispanic pregnant women
Methods	RCT, cross-over, single blind (investigator). Location: USA.
Participants	Estimated enrolment 20 overweight or obese pregnant Hispanic women between 30 and 36 weeks' gestation Excluded if diagnosis of GDM, pre-existing diabetes mellitus, renal disease, thyroid disease, cardiovascular disease, history of drug abuse, nut allergies
Interventions	Almond meal (bagel, almond butter and apple juice) vs bagel with cream cheese and apple juice
Outcomes	Markers for glucose intolerance, serum triglyceride concentrations. Secondary: Metabolic markers, glucose, insulin, hormonal and inflammatory markers, satiety markers
Starting date	September 2011.
Contact information	Lisa R Sawrey-Kubicek, MS, RD, lsawreykubicek@chori.org, Children's Hospital & Research Center Oakland
Notes	Estimated completion date: December 2013. Emailed 25/9/14.

Ko 2010

Trial name or title	Effect of physical activity on metabolic syndrome in pregnancy and fetal outcome
Methods	RCT, single blind (investigator).
Participants	Location: United States, Washington. Target number of participants: 100. Inclusion criteria: pregnant women 18-45 years old receiving prenatal care at MAMC Exclusion criteria: women do not have a gallbladder, do not speak English, over 14 weeks pregnant at study entry, do not plan to deliver at MAMC, have medical contraindications, unwilling to participate in exercise

Ko 2010 (Continued)

	intervention program, < 18 years of age, currently engaged in a regular vigorous-exercise program
Interventions	Intervention group will exercise 3 times per week at moderate-vigorous intensity for 45 minutes per session through their 36 week of pregnancy Control group women will continue their usual physical activity throughout pregnancy
Outcomes	Primary outcome: central adiposity. Secondary outcomes: leptin levels, glucose insulin, cholesterol, fetal adiposity, neonatal adiposity
Starting date	October 2007.
Contact information	Cynthia W Ko, University of Washington.
Notes	

Laitinen 2013

Trial name or title	Placebo-controlled intervention study for maternal and child health
Methods	RCT, parallel, double blind placebo-controlled. Location: Finland.
Participants	Estimated enrolment: 440 overweight healthy pregnant women less than 16 weeks' gestation Excluded if diabetes, coeliac disease, hypo-/hyperthyroidism, increased bleeding tendency
Interventions	Dietary supplement (comparison of probiotics, fish oil and their combination) vs placebo
Outcomes	GDM, fasting glucose levels, prevalence of allergy in child. Secondary: management of GDM, body composition, immunologic and metabolic markers, fecal microbiota
Starting date	September 2013.
Contact information	
Notes	Estimated primary completion date: March 2016 (final data collection date for primary outcome measure)

Li 2011

Trial name or title	Effects of dietary and lifestyle interventions in obese pregnant women from the first trimester on gestational weight gain and pregnancy outcomes
Methods	RCT, parallel, single blind (participant). Location: China.
Participants	373 overweight or obese pregnant women gestational age between 6 and 12 weeks of gestation, pre-pregnancy ≥ 28 (kg/m ²) aged ≥ 18 years, and a singleton pregnancy Excluded if prediabetes and diabetes, hypertension, chronic renal disease, thyroid disorder, gestational weeks

Li 2011 (Continued)

	≥ 13, multiple pregnancy, uterine malformation, physical restriction that prevents exercise
Interventions	Dietary and lifestyle intervention (individualised dietary intake protocol - standard care intensive dietary and lifestyle intervention from first trimester to delivery, every 2-4 weeks) vs standard care
Outcomes	GWG, from enrolment to delivery (28-34 weeks of gestation), GDM, hypertensive disorders, large-for-gestational-age infants, macrosomia, caesarean section
Starting date	01/04/2011.
Contact information	
Notes	Emailed 25/9/14.

Liu 2011

Trial name or title	Magnesium supplementation in the second trimester of pregnancy to overweight and obese individuals
Methods	RCT, 3-arm, parallel, double blind. Location: USA.
Participants	Estimated enrolment: 60 overweight and obese pregnant women in their first trimester between 18 and 40 years of age Excluded if on insulin therapy or other oral hypoglycaemic agents, multiple gestation, baseline HgbA1C > 6.5%, prior history of clinically diagnosed T2D, multiple dietary restrictions/food allergies, heart, renal, or liver failure, clinical history of psychiatric illness or substance abuse and other exclusions
Interventions	Group A will receive oral magnesium citrate, group B will receive dietary counselling about following a magnesium rich diet) vs group C who will receive a placebo (control)
Outcomes	Maternal biomarkers, blood and urine markers, neonatal birthweight/height, macrosomia, preterm birth, head circumference, and Apgar score and more
Starting date	01/01/2012.
Contact information	Simin Liu, Dr, no email given, University of California, Los Angeles
Notes	

McAuliffe 2013

Trial name or title	Pregnancy, exercise and nutrition research study with app support
Methods	Single centre RCT. Location: Ireland.

McAuliffe 2013 (Continued)

Participants	500 women with singleton pregnancies between 10-15 weeks' gestation between the ages of 18-45 with a smart-phone, and a BMI of greater than 25 kg/m ² Excluded if pre-gestational diabetes or early onset gestational diabetes or past history of gestational diabetes, and other exclusions
Interventions	Women in the intervention group will have standard antenatal care but will receive a 'healthy lifestyle package with app support' (a combination of a healthy diet, an exercise intervention with a smart phone application as an information and motivational source) vs controls who will receive a 'regular lifestyle package' consisting of standard antenatal care and general advice on weight gain according to BMI
Outcomes	Gestational diabetes, GWG, glycaemic index, PA levels.
Starting date	01/01/2013.
Contact information	Professor Fionnuala McAuliffe fionnuala.mcauliffe@ucd.ie
Notes	Estimated completion date: 2016 (personal communication on 25/9/14)

Moholdt 2011

Trial name or title	Exercise training in pregnancy for obese women (ETIP): study protocol for a RCT
Methods	RCT, parallel, blinded. Location: Norway.
Participants	150 previously sedentary obese pregnant women with singleton live fetus at an 11-14 weeks ultrasound scan Excluded if pregnancy complications, high risk for preterm labour or diseases that could interfere with participation, and habitual exercise training
Interventions	Physical exercise (60 mins up to 4 times per week starting in gestation week 14) vs standard antenatal care
Outcomes	GWG, exercise capacity, endothelial function, physical activity level, body composition, serum markers of cardiovascular risk, incontinence, lumbopelvic pain and cardiac function, anthropometric variables at birth, Apgar score, serum markers of inflammation and metabolism in cord blood
Starting date	01/09/2010.
Contact information	Trine T Moholdt, trine.moholdt@ntnu.no, Norwegian University of Science and Technology
Notes	Estimated completion date: 2016 (personal communication on 25/9/14)

Nagle 2011

Trial name or title	Continuity of midwifery care and gestational weight gain in obese women
Methods	RCT.
Participants	214 primiparous women attending 1 of the study hospitals for maternity care with a booking BMI > 30 and less than 17 weeks' gestation. Exclusion criteria include inability to speak English, multiple pregnancy, vaginal bleeding or serious medical condition
Interventions	Continuity of midwifery care compared with routine management
Outcomes	GWG; women's experience of care and satisfaction with care; psychological well being
Starting date	Not clear.
Contact information	cate.nagle@deakin.edu.au
Notes	Emailed 25/9/14.

Nagle 2013

Trial name or title	Primary prevention of gestational diabetes for women who are overweight and obese: a RCT
Methods	RCT, not blinded. Location: Australia.
Participants	Pregnant women who are overweight or obese, with a singleton pregnancy, less than 14 weeks' gestation and recruited from the Barwon South West region of Victoria, Australia. Excluded: with pre-existing diabetes, a past history of gestational diabetes, currently experiencing vaginal bleeding or with severe medical conditions
Interventions	Behavioural counselling: (EDGE program from recruitment until birth, consisting of weekly contact with a brief (5-minute) phone call each fortnight) vs usual care
Outcomes	GDM, GWG, LGA, psychological health and more.
Starting date	Not stated.
Contact information	Cate Nagle, cate.nagle@deakin.edu.au, Deakin University.
Notes	Emailed 25/9/14.

Norman 2012

Trial name or title	Efficacy of metformin in pregnant obese women: a RCT.
Methods	RCT, multicentre, placebo-controlled. Location: UK.

Norman 2012 (Continued)

Participants	Caucasian obese pregnant women between 12-0 and 16+0 weeks' gestation Excluded if non-Caucasian, gestation greater than 16 weeks, pre-existing diabetes, gestational diabetes in a previous pregnancy, systemic disease requiring regular medication, gestational diabetes in index pregnancy prior to randomisation, previous delivery of a baby less than 3rd centile or previous pregnancy with pre-eclampsia prompting delivery before 32 weeks' gestation and more
Interventions	Medicinal (oral metformin tablets given 3 times daily to a maximum of 500 - 2500 mg daily) vs placebo
Outcomes	Gestational age and sex adjusted birthweight centiles of the baby, correlation between maternal insulin resistance, adverse pregnancy outcomes. Neonatal body composition, biological mechanisms of metformin, maternal anthropometry and more
Starting date	01/02/2011.
Contact information	Prof Jane Norman, jane.norman@ed.ac.uk, University of Edinburgh
Notes	Estimated end date: 30/11/2013.

Parat 2010

Trial name or title	Impact of education during pregnancy in overweight pregnant women (ETOIG)
Methods	RCT. Masking: single blind (participant).
Participants	Location: Hospital Necker Paris, France. Target number of participants: 800. Inclusion criteria: pregnant women who agree the study, BMI > 25 kg/m ² (BMI is based on retrospective self reported weight of the patient before pregnancy), no more than 21 weeks of gestation Exclusion criteria: younger than 18 years, multiple gestation, high-risk pregnancy, psychiatric pathology, diabetes diagnosed before the inclusion, fetal malformation, history of obesity surgery, no understanding of French language, planning to move to another area
Interventions	Intervention: therapeutic education; intensive training individual and collective teaching Control: placebo comparator; classical follow-up with 2 individual consultations
Outcomes	Primary outcomes: -30% reduction of rapid infancy weight gain at 2 years defined as > + 0.67 change in weight SD score. The 0.67 SD represents the difference between the displayed centile lines on standard infant growth charts Secondary outcomes: -reduction of rapid infancy weight gain between 0 and 6 months; -reduction of the number of children with BMI over 19 at 2 years; -reduction of incidence of gestational diabetes, pre-eclampsia, HTA during pregnancy, caesarean, fetal macrosomia; -reduction of spontaneous feeding at 4 months; -increase of breastfeeding (number of women and duration); -reduction 1 and 2 years after pregnancy of mother weight and BMI (except 2nd pregnancy);

Parat 2010 (Continued)

	-reduction of abnormality of lipid and glycaemia test in women, 2 years after the pregnancy
Starting date	September 2008.
Contact information	Sophie Parat; sophie.parat@nck.aphp.fr Raphael Serreau; raphael.serreau@cch.aphp.fr
Notes	

Peccei 2010

Trial name or title	Nutrition intervention for the promotion of healthy weight gain during pregnancy: the Revere pregnancy weight management study
Methods	RCT, parallel, open label. Location: USA.
Participants	300 overweight or obese pregnant women ages 18 to 49 at the first prenatal visit < 16 weeks' gestation who have and have not dieted in the past Excluded if multiple gestation, diabetes prior to pregnancy, medical history of an eating disorder and other exclusions
Interventions	Nutrition counselling (twice monthly interaction with a registered dietitian from 6-16 weeks' gestation through 6 months postpartum) vs current standard of optimal care in addition to 1 nutrition education session with the study nutritionist at 6-16 weeks' gestation
Outcomes	GWG, intake of nutritious foods, hypertension and eclampsia, gestational diabetes, caesarian delivery, macrosomia, admission to neonatal intensive care unit and others
Starting date	01/12/2009.
Contact information	Alessandra Peccei, MD, Massachusetts General Hospital.
Notes	Estimated completion date: January 2015.

Rauh 2014

Trial name or title	Rauh K, KuHealthy living in pregnancy: a cluster-randomised controlled trial to prevent excessive gestational weight gain - rationale and design of the GeliS study
Methods	A prospective, cluster-randomised, controlled, open intervention trial
Participants	2500 pregnant women. Inclusion criteria: women aged 18 to 43 years with a singleton pregnancy, a pre-pregnancy BMI ≥ 18.5 kg/m ² and ≤ 40 kg/m ² , and sufficient German language skills are eligible for the study. These pregnant women are recruited before the 12th week of gestation Exclusion criteria: multiple pregnancy, high-risk pregnancy prohibiting study participation (contraindications to exercise e.g. placenta praevia, persistent bleeding, cervical incompetence etc.), prepregnancy diabetes

Rauh 2014 (Continued)

	mellitus or early gestational diabetes, uncontrolled chronic diseases (e.g. thyroid dysfunction), psychiatric or psychosomatic diseases, and any other diseases which could interfere with compliance according to the study protocol
Interventions	Behavioural: lifestyle intervention. The intervention program consists of 4 individual counselling modules focusing on diet, physical activity and weight monitoring (12th-16th, 16th-20th, 30th-34th week of gestation and 6th-8th week postpartum). The counselling sessions are given by carefully trained midwives or medical staff in combination with prenatal visits and follow a standardised curriculum. Women are provided with brochures including a list of adequate prenatal exercise programs and a pedometer. Furthermore, they receive a chart personalised according to their baseline BMI category to monitor weight development
Outcomes	Primary outcomes -GWG. -Proportion of pregnant women showing excessive GWG according to IOM guidelines Secondary outcomes -Incidence of gestational diabetes (24th-28th week of gestation, via an OGTT) glycosylated haemoglobin concentration (30th-34th week of gestation) -Other pregnancy complications such as pre-eclampsia. -Anthropometric measures and health status of the newborns (birthweight, height, head circumference, LGA, SGA, Apgar score, pH) -Obstetric complications (mode of delivery, induction of labour, rate of caesarean sections, etc.)
Starting date	September 2013.
Contact information	Kathrin Rauh, M.Sc. kathrin.rauh@KErn.bayern.de
Notes	Estimated completion date: September 2018.

Redman 2012

Trial name or title	Expecting success: personalised management of body weight during pregnancy
Methods	RCT, parallel, open label. Location: USA.
Participants	306 overweight or obese pregnant women between 18 and 40 years old before 12 weeks of your pregnancy Excluded if pregnant with more than 1 infant, habitually smoke, abuse illegal or prescription drugs in the last 6 months, consume more than 2 alcoholic drinks per week, history of: 3 or more first trimester miscarriages, high blood pressure, type 1 diabetes, pregnancy related diabetes during screening, HIV or AIDS, psychotic disorder, major depressive episode, bipolar disorder or eating disorders and other exclusions
Interventions	Behavioural counselling (weight management counselling up to 4 times per month at clinic, plus 2 telephonic sessions) vs physician directed care
Outcomes	GWG. PA, diet, postpartum weight retention.
Starting date	01/12/2012.

Redman 2012 (Continued)

Contact information	Loren Johnson, BS, MS, loren.johnson@pbrc.edu, Pennington Biomedical Research Centre
Notes	Estimated completion date: June 2016.

Roberts 2012

Trial name or title	Interventions to reduce excess weight gain in pregnancy in overweight and obese mothers
Methods	RCT, parallel, open label. Location: USA.
Participants	75 over weight or obese pregnant women age 18-45 years in first trimester of pregnancy Excluded if carrying multiple fetuses, GDM at study entry, Type 2 diabetes mellitus or blood glucose > 125 mg/dL at screening, current substance abuse, smoker, alcohol consumption of more than 1 drink per day, pre-existing medical conditions or use of medications
Interventions	Diet counselling (Group based counselling plus Fiber Cereal or resistant starch) vs routine clinical care and no additional interventions
Outcomes	Maternal and infant body weight change, maternal non-fasting weight, infant weight. Infant outcomes: body composition, Apgar, dietary intake. Maternal and perinatal outcomes: caesarean deliveries, gestational hypertension/pre-eclampsia, preterm birth, birth complications, fasting blood glucose and insulin concentrations throughout pregnancy
Starting date	01/07/2012.
Contact information	Contact: Lorie E Urban, Ph.D, PregWeight@tufts.edu, Tufts University
Notes	May 2014 (final data collection date for primary outcome measure)

Seneviratne 2014

Trial name or title	Antenatal exercise in overweight and obese women and its effects on offspring and maternal health: design and rationale of the IMPROVE (Improving Maternal and Progeny Obesity Via Exercise) RCT
Methods	A 2-arm parallel RCT. Location: Auckland, New Zealand.
Participants	100 pregnant women aged 18 to 40 years with a BMI ≥ 25 kg/m ² who are carrying a singleton fetus less than 20 weeks of gestation, with gestation confirmed by a dating scan early in pregnancy, and who are resident in the Auckland region are eligible for the trial. Exclusion criteria include ongoing smoking during the current pregnancy or contra-indications to aerobic exercise in pregnancy as stated by ACOG
Interventions	The exercise regimen consists of home-based stationary cycling at 20 weeks of gestation. The 16-week exercise regimen consists of 67 exercise sessions, comprising approximately 1500 minutes of moderate-intensity exercise. The frequency and duration of prescribed exercise varies over the intervention period. The intervention commences with 3 exercise sessions per week and increases to 5 sessions per week. All exercise sessions

	commence with a 5-minute warm-up on the stationary cycle at low intensity, maintaining heart rate below target rate, and concludes with a similar 5-minute cool down. The duration of moderate-intensity exercise at prescribed heart rate increases gradually from 15 minutes to 30 minutes per session and gradually decreases again from 33 weeks of gestation while maintaining the frequency at 5 per week. A qualified exercise physiologist maintains regular contact with the exercising participants via phone, email, and home visits. To increase compliance with exercise, if cycling becomes unacceptable or uncomfortable with advancing pregnancy, participants are encouraged to utilise an alternative forms of exercise such as brisk walking, while maintaining same heart rate intensity, frequency, and duration during exercise
Outcomes	Primary outcome: offspring birthweight. Secondary outcomes: offspring outcomes include neonatal anthropometry and body composition, fetal growth measures, cord blood metabolic markers and newborn complications including rates of LGA (birthweight > 90 th centile) and SGA (birthweight < 10 th centile) babies. Maternal outcomes include weight gain, aerobic fitness, quality of life, metabolic markers, postpartum weight and body composition, as well as pregnancy and delivery outcomes including timing and mode of delivery and length of hospital stay
Starting date	01/10/2012.
Contact information	Sumudu N Seneviratne (s.seneviratne@auckland.ac.nz).
Notes	

Shen 2010

Trial name or title	Impact of diet and exercise activity on pregnancy outcomes (IDEA)
Methods	Randomised, open label.
Participants	Location: Canada. Inclusion criteria: age 18 years and older, pregnancy < 20 weeks, expressed interest in study and willingness to consent to participate in the study Exclusion criteria: obstetric or medical contraindications for exercise according to 2002 SOCG guideline (ruptured membranes, preterm labour, incompetent cervix, hypertensive disorders of pregnancy, growth restricted fetus, placenta previa, persistent bleeding in 2nd or 3rd trimester, significant metabolic, cardiovascular, respiratory or systemic disorder), pre-existing diabetes (except a history of GDM, but not in current pregnancy), multiple gestations
Interventions	A community-based exercise and dietary intervention.
Outcomes	Primary outcomes: excessive weight gain during pregnancy. Secondary outcomes: macrosomia, requirement of delivery procedures
Starting date	July 2006.
Contact information	Garry Shen; gshen@ms.umanitoba.ca University of Manitoba.
Notes	

Skouteris 2012

Trial name or title	A RCT of a specialised health coaching intervention to prevent excessive gestational weight gain and post-partum weight retention in women: the HIPPP study
Methods	RCT. Location: Australia.
Participants	220 women who have a BMI > 18.5 are 18 years of age or older, English speaking, no history of disordered eating or diabetes and are less than 18 weeks' gestation at recruitment
Interventions	Behavioural counselling (1-on-1 sessions with a Health Coach, and 2 by 2 hour educational group sessions led by a Health Coach) vs education alone (2 by 2 hour educational group sessions with no HC components)
Outcomes	BMI, waist circumference, psychological factors.
Starting date	Not stated.
Contact information	Helen Skouteris, helen.skouteris@deakin.edu.au, Deakin University, Melbourne
Notes	Publication pending (personal communication on 25/9/14).

Smith 2010

Trial name or title	The design of a community lifestyle programme to improve the physical and psychological well-being of pregnant women with a BMI of 30 kg/m ² or more
Methods	RCT.
Participants	Location: England. Enrolment: 400 (200 from each area). Inclusion criteria: women attending for antenatal care in a 2 UK hospitals with a BMI 30 kg/m ² or greater Exclusion criteria: aged under 18, intend to move in the next 3 months, take weight control medication or if they have any cautions for starting exercise (this will be determined using the Revised Physical Activity Readiness Questionnaire (PARQ) and the Royal College of Obstetricians and Gynaecologists (RCOG) recommendations)
Interventions	The lifestyle programme will run for 1.5 hours per week for 10 weeks and is supplementary to standard antenatal care. Women will be invited to the 10-week programme at any stage before 30 weeks' gestation to ensure completion of the programme before their delivery The control group will receive routine care.
Outcomes	Primary outcomes: pregnancy weight gain, birthweight, mode of birth, and method of infant feeding at hospital discharge; psychological outcomes include self-efficacy, well-being, and goal attainment Secondary outcomes: women's experience of pregnancy and healthcare services, amount of physical activity, food intake, and the suitability of the intervention components
Starting date	October 2011 (recruitment).

Contact information	Professor Tina Lavender; tina.lavender@manchester.ac.uk University of Manchester, Oxford Road, Manchester. M13 9PL United Kingdom.
Notes	Publication pending (personal communication on 25/9/14).

Thangaratinam 2014

Trial name or title	Effect of simple, targeted diet in pregnant women with metabolic risk factors on pre-eclampsia (ESTEEM): a randomised trial
Methods	RCT, location: United Kingdom.
Participants	3640 pregnant women. Inclusion criteria: pregnant women less than 18 weeks of gestation with at least 1 of the following: i. BMI ≥ 30 kg/m ² ii. Raised serum triglycerides ≥ 1.7 mmol/L iii. Raised blood pressure of systole ≥ 140 mm Hg or diastole ≥ 90 mm Hg Exclusion criteria: i. BMI < 18.5 kg/m ² or ≥ 40 kg/m ² ii. Women on lipid altering drugs iii. History of diabetes iv. Chronic renal disease v. Auto immune disease vi. Multiple pregnancy vii. Poor understanding of written and spoken English viii. Not able to follow Mediterranean diet for religious or other reasons ix. < 16 years of age x. Not able to consume nuts or extra virgin olive oil
Interventions	Behavioural: targeted ESTEEM diet. The key components of the diet are: High intake of vegetables, nuts, non-refined grains, legumes and fruits; moderate-to-high consumption of fish; small-to-moderate intake of poultry and dairy products such as yoghurt and cheese; low consumption of red meat and processed meat and avoidance of sugary drinks, fast food and high fat food; high fibre; intake of nuts including walnuts and almonds that are rich sources of monounsaturated and polyunsaturated fatty acids (30 g/day); olive oil to cook and dress salads as the main source of fat (0.5 L/week) The intervention will include structured meal plans and grocery lists, recipes for healthy diet and appropriate choices at restaurants
Outcomes	Number of participants with a diagnosis of pre-eclampsia. Diagnosis of pre-eclampsia defined as: new onset hypertension after 20 weeks' gestation defined as SBP ≥ 140 mm Hg or DBP ≥ 90 mmHg, in at least 2 readings AND new onset proteinuria defined as spot urine Protein/creatinine ratio test greater than 30 mg/mmol or > 24 -hour urine 300 mg/24 hours or 2+ or more on standard urinary dipstick tests after 20 weeks' gestation Superimposed pre-eclampsia in women with chronic hypertension or chronic proteinuria Women with eclamptic seizures with no hypertension or proteinuria
Starting date	July 2014.
Contact information	Shakila Thangaratinam, s.thangaratinam@qmul.ac.uk
Notes	Estimated primary completion date: February 2016.

Thomson 2014

Trial name or title	Delta Healthy Sprouts: a randomised comparative effectiveness trial to promote maternal weight control and reduce childhood obesity in the Mississippi Delta
Methods	Parallel arm RCT. Location: USA.
Participants	150 mothers and their infants residing in the rural Mississippi Delta who are in their second trimester and are < 19 weeks pregnant with first, second or third child, > 18 years of age between 14 and 18 weeks' gestation. Excluded if multiple pregnancy
Interventions	Nutrition and PA counselling (monthly PaT lessons and materials and PaTE supplemental nutrition and physical activity lessons and materials) vs monthly PaT lessons and materials only
Outcomes	Primary: mothers: GWG, BMI. Infants: weight-for-length. Secondary; diet, diet quality, physical activity, knowledge, beliefs, and practices
Starting date	January 2013.
Contact information	Jessica L Thomson, jessica.thomson@ars.usda.gov, United States Department of Agriculture/University of Illinois at Chicago and University of Illinois Cancer Centre
Notes	

Uauy 2013

Trial name or title	Effectiveness of a normative intervention (diet, physical activity and breastfeeding) on maternal nutrition and offspring growth and development: nutrition in the first 1000 days key to healthy growth and long-term health
Methods	Cluster-RCT, multicentre, single group, double blind (investigator, outcomes assessor) Location: Chile.
Participants	2400 pregnant women before 15 weeks of pregnancy who are not planning to move in the next 2 years Excluded if women were classified as high risk according to the norms of the Chilean Ministry of Health (MoH) and/or underweight (BMI < 18.5)
Interventions	Diet and physical activity counselling-support and breastfeeding promotion till 12 months postpartum vs routine care
Outcomes	GWG, glycaemic control, weight retention at 12 months, infant growth
Starting date	01/09/2013.
Contact information	Maria L Garmendia, PhD, mgarmendia@inta.uchile.cl, University of Chile
Notes	Estimated completion date: March 2017.

Vistad 2009

Trial name or title	Fit For Delivery: a study of the effect of exercise intervention and nutritional counselling on pregnancy outcome
Methods	RCT, parallel, single blinded (investigator). Location: Norway.
Participants	600 pregnant women expecting first child who reside in 1 of the following towns: Kristiansand, Søgne, Sogndalen, Vennesla, Lillesand, Mandal, in their gestational weeks 12-20 Excluded if twin or other multiple pregnancy, pre-existing diabetes, physical handicap which precludes participation in exercise groups, ongoing drug addiction, serious mental disorder, BMI at or below 19 before pregnancy, inability to read/write Norwegian or English
Interventions	Diet counselling (2 telephone consultations on nutritional health and access to Internet topics) and twice weekly exercise groups vs routine pregnancy care
Outcomes	GWG, birthweight, maternal fasting serum glucose level, incidence of operative delivery, both caesarean section and operative vaginal delivery, maternal body composition. Secondary: maternal weight retention, measurement of serum levels of hormones which regulate serum glucose levels, in both the pregnant woman and her new-born baby, incidence of women with serum glucose levels >7.8 mmol/L after 2-hour glucose challenge test
Starting date	01/09/2009.
Contact information	Ingvild Vistad, MD, PhD, no email mentioned, Sorland Hospital HF
Notes	Estimated completion date: December 2014.

Yan 2012

Trial name or title	Low glycaemic index diet intervention on insulin resistance of overweight pregnant women
Methods	RCT, parallel, single blind (participant). Location: China.
Participants	400 pregnant women with first prenatal examination BMI equal to or greater than 24 kg/m ² , singleton pregnancy, uniparous, 18 years to 45 years, ≥ 12 weeks' gestation. Excluded if artificial impregnation, history of hypertension, diabetes, coronary heart disease or mental disorder, special diet habit
Interventions	Diet counselling (Dietary Guidelines for Chinese residents for pregnant women and low glycaemic index diet) vs standard diet counselling (diet counselling based on Dietary guidelines for Chinese Residents)
Outcomes	Maternal insulin, cord blood C-peptide, incidence of gestational diabetes, macrosomia. Secondary: incidence of gestational hypertension, proportion of women with newly incident hypertension during pregnancy, birth-weight, caesarean delivery, gestational age
Starting date	01/02/2012.
Contact information	Weili Yan, no email given, Fudan University.

Notes	November 2014 (final data collection date for primary outcome measure)

ACOG: the American Congress of Obstetricians and Gynecologists
 BMI: body mass index
 DBP: diastolic blood pressure
 GDM: gestational diabetes mellitus
 GL: glycaemic load
 GWG: gestational weight gain
 HbA1c: haemoglobin A1c
 HDL: high density lipoprotein
 HIV: human immunodeficiency virus
 HTA: hydrothermal endometrial ablation
 IOM: Institute of Medicine
 LGA: large-for-gestational age
 MAMC: Madigan Army Medical Center
 OGTT: oral glucose tolerance test
 PA: physical activity
 QoL: quality of life
 RCT: randomised controlled trial
 SBP: systolic blood pressure
 SD: standard deviation
 SOCG: the Society of Obstetricians and Gynaecologists of Canada
 T2D: Type 2 diabetes
 WHO: World Health Organization

DATA AND ANALYSES

Comparison 1. All diet and/or exercise interventions vs standard/other care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Excessive weight gain	24	7096	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.73, 0.87]
1.1 Diet intervention (low GI diet)	2	835	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.66, 0.91]
1.2 Diet and exercise counselling	9	3144	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.75, 0.98]
1.3 Unsupervised exercise	3	603	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.71, 0.97]
1.4 Supervised exercise	3	1298	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.63, 0.89]
1.5 Supervised exercise and diet	5	689	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.59, 0.85]
1.6 Diet counselling/other	3	527	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.17, 1.23]
2 Weight gain (kg)	36		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Diet intervention (low GI diet)	5		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Diet and exercise counselling	13		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Unsupervised exercise	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Supervised exercise intervention	7		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.5 Supervised exercise plus diet intervention	3		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.6 Diet counselling/other	7		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Low weight gain	11	4422	Risk Ratio (M-H, Random, 95% CI)	1.14 [1.02, 1.27]
3.1 Diet intervention (low GI diet)	1	87	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.64, 2.43]
3.2 Diet and exercise counselling	5	2552	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.90, 1.75]
3.3 Unsupervised exercise	3	603	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.80, 1.60]
3.4 Supervised exercise	1	962	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.99, 1.48]
3.5 Supervised exercise plus diet	1	49	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.40, 5.50]
3.6 Diet counselling/other	1	169	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.80, 1.82]
4 Preterm birth	16	5923	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.68, 1.22]
4.1 Diet intervention (low GI diet)	2	804	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.11, 1.02]
4.2 Diet and exercise counselling	7	3170	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.60, 1.51]
4.3 Unsupervised exercise	2	229	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.35, 3.85]
4.4 Supervised exercise	3	1129	Risk Ratio (M-H, Random, 95% CI)	1.92 [0.75, 4.93]
4.5 Diet counselling/other	3	591	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.26, 1.73]
5 Pre-eclampsia	15	5330	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.77, 1.16]
5.1 Diet and exercise counselling	7	3139	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.74, 1.31]

5.2 Supervised exercise	2	1024	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.52, 1.60]
5.3 Unsupervised exercise	2	229	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.38, 6.73]
5.4 Supervised exercise plus diet	1	304	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.51, 1.40]
5.5 Diet counselling/other	4	634	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.54, 1.48]
6 Hypertension (not prespecified)	11	5162	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.51, 0.96]
6.1 Diet and exercise counselling	5	2648	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.54, 1.29]
6.2 Unsupervised exercise	2	229	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.12, 1.54]
6.3 Supervised exercise	3	1749	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.29, 1.03]
6.4 Supervised exercise plus diet	1	304	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.51, 1.40]
6.5 Diet counselling/other	1	232	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.08, 1.06]
7 Induction of labour	8	3832	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.94, 1.19]
7.1 Diet intervention (low GI diet)	1	734	Risk Ratio (M-H, Random, 95% CI)	1.64 [1.14, 2.36]
7.2 Diet and exercise counselling	4	2522	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.93, 1.14]
7.3 Unsupervised exercise	1	192	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.65, 1.48]
7.4 Supervised exercise	1	35	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.26]
7.5 Diet counselling/other	2	349	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.59, 1.35]
8 Caesarean delivery	28	7534	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.88, 1.03]
8.1 Diet intervention (low GI diet)	2	133	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.33, 3.01]
8.2 Diet and exercise counselling	9	3406	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.75, 1.01]
8.3 Unsupervised exercise intervention	2	229	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.53, 1.59]
8.4 Supervised exercise	8	2405	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.82, 1.11]
8.5 Supervised exercise plus diet	3	607	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.69, 1.45]
8.6 Diet counselling/other	5	754	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.93, 1.21]
9 Postpartum weight retention (kg)	7	818	Mean Difference (IV, Random, 95% CI)	-1.12 [-2.49, 0.25]
9.1 Diet intervention (low GI diet)	1	414	Mean Difference (IV, Random, 95% CI)	-1.40 [-2.63, -0.17]
9.2 Diet and exercise counselling	2	188	Mean Difference (IV, Random, 95% CI)	-1.13 [-4.88, 2.61]
9.3 Supervised exercise	2	132	Mean Difference (IV, Random, 95% CI)	0.17 [-1.61, 1.96]
9.4 Supervised exercise plus diet	1	49	Mean Difference (IV, Random, 95% CI)	-0.80 [-2.84, 1.24]
9.5 Diet counselling/other	1	35	Mean Difference (IV, Random, 95% CI)	-6.9 [-15.28, 1.48]
10 Postpartum weight retention (n/N; investigator defined time frame)	5	902	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.63, 0.97]
10.1 Diet and exercise counselling	3	615	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.51, 1.01]
10.2 Supervised exercise plus diet intervention	2	287	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.66, 1.10]
11 Energy intake (kj)	12	4065	Mean Difference (IV, Random, 95% CI)	-570.77 [-894.28, -247.26]

11.1 Diet intervention (low GI diet)	4	1462	Mean Difference (IV, Random, 95% CI)	-297.26 [-562.80, -31.72]
11.2 Diet and exercise counselling	4	2190	Mean Difference (IV, Random, 95% CI)	-897.66 [-1763.09, -32.23]
11.3 Supervised exercise plus diet intervention	3	274	Mean Difference (IV, Random, 95% CI)	-1090.80 [-2263.86, 82.26]
11.4 Diet counselling/other	1	139	Mean Difference (IV, Random, 95% CI)	-172.0 [-686.85, 342.85]
12 Fibre intake (g)	8	3466	Mean Difference (IV, Random, 95% CI)	1.53 [0.94, 2.12]
12.1 Diet intervention (low GI diet)	4	1223	Mean Difference (IV, Random, 95% CI)	1.35 [0.55, 2.15]
12.2 Diet and exercise counselling	2	1996	Mean Difference (IV, Random, 95% CI)	1.97 [0.95, 2.99]
12.3 Supervised exercise plus diet intervention	1	112	Mean Difference (IV, Random, 95% CI)	1.0 [-3.06, 5.06]
12.4 Diet counselling/other	1	135	Mean Difference (IV, Random, 95% CI)	1.10 [-0.91, 3.11]
13 Physical activity score (26-29 weeks)	9	2851	Std. Mean Difference (IV, Random, 95% CI)	0.40 [0.18, 0.61]
13.1 Diet and exercise counselling	5	2395	Std. Mean Difference (IV, Random, 95% CI)	0.27 [0.03, 0.51]
13.2 Supervised exercise intervention	2	232	Std. Mean Difference (IV, Random, 95% CI)	0.43 [0.06, 0.79]
13.3 Supervised exercise plus diet intervention	2	224	Std. Mean Difference (IV, Random, 95% CI)	0.73 [0.46, 1.00]
14 Macrosomia Infant birthweight > 4000 g	27	8598	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.86, 1.02]
14.1 Diet intervention (low GI diet)	4	1472	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.84, 1.10]
14.2 Diet and exercise counselling	10	3705	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.77, 1.12]
14.3 Unsupervised exercise	2	229	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.74, 1.81]
14.4 Supervised exercise intervention	7	2445	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.64, 1.02]
14.5 Supervised exercise plus diet intervention	3	398	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.71, 1.46]
14.6 Diet counselling/other	2	349	Risk Ratio (M-H, Random, 95% CI)	1.81 [0.88, 3.72]
15 Infant birthweight > 90th centile	18	4525	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.80, 1.05]
15.1 Diet and exercise counselling	6	2777	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.74, 1.02]
15.2 Unsupervised exercise	1	192	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.34, 3.43]
15.3 Supervised exercise intervention	4	397	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.59, 2.00]
15.4 Supervised exercise plus diet intervention	3	607	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.67, 1.66]
15.5 Diet intervention (low GI diet)	3	200	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.50, 3.11]
15.6 Diet counselling/other	2	352	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.54, 1.69]
16 Birthweight (g) (not prespecified)	29	8350	Mean Difference (IV, Random, 95% CI)	12.20 [-15.26, 39.65]

16.1 Diet intervention (low GI diet)	4	1447	Mean Difference (IV, Random, 95% CI)	-0.84 [-1.16, -0.52]
16.2 Diet and exercise counselling	9	3516	Mean Difference (IV, Random, 95% CI)	52.33 [-33.23, 137.89]
16.3 Unsupervised exercise	1	37	Mean Difference (IV, Random, 95% CI)	-124.21 [-435.86, 187.44]
16.4 Supervised exercise	11	2714	Mean Difference (IV, Random, 95% CI)	16.27 [-38.56, 71.11]
16.5 Supervised exercise and diet	1	49	Mean Difference (IV, Random, 95% CI)	-107.0 [-343.33, 129.33]
16.6 Diet counselling/other	3	587	Mean Difference (IV, Random, 95% CI)	1.40 [-78.04, 80.84]
17 Infant birthweight < 2500 g	12	4834	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.67, 1.14]
17.1 Exercise and diet counselling	5	2934	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.60, 1.17]
17.2 Unsupervised exercise	2	229	Risk Ratio (M-H, Random, 95% CI)	2.14 [0.24, 18.80]
17.3 Supervised exercise	4	1387	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.61, 1.63]
17.4 Supervised exercise plus diet	1	49	Risk Ratio (M-H, Random, 95% CI)	2.67 [0.11, 62.42]
17.5 Diet counselling/other	1	235	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.29, 1.53]
18 Infant birthweight < 10th centile	7	662	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.61, 1.94]
18.1 Diet intervention (low GI diet)	2	155	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.47, 4.71]
18.2 Diet and exercise counselling	2	207	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.28, 3.29]
18.3 Supervised exercise	3	300	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.45, 2.19]
19 Shoulder dystocia	4	3253	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.57, 1.83]
19.1 Diet intervention (low GI diet)	1	759	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.10, 2.82]
19.2 Diet and exercise counselling	1	2142	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.81, 1.93]
19.3 Diet counselling/other	2	352	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.05, 2.64]
20 Neonatal hypoglycaemia	4	2601	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.76, 1.18]
20.1 Diet and exercise counselling	2	2256	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.79, 1.32]
20.2 Diet counselling/other	2	345	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.36, 2.15]
21 Birth trauma	2	2256	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.35, 2.30]
21.1 Diet and exercise counselling	2	2256	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.35, 2.30]
22 Neonatal hyperbilirubinaemia	2	2256	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.62, 1.10]
22.1 Diet and exercise counselling	2	2256	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.62, 1.10]
23 Neonatal respiratory distress syndrome	2	2256	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.26, 0.85]
23.1 Diet and exercise counselling	2	2256	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.26, 0.85]
24 Postpartum hemorrhage	2	2901	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.78, 1.14]
24.1 Diet intervention (low GL diet)	1	759	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.23, 3.08]
24.2 Diet and exercise counselling	1	2142	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.78, 1.14]

Comparison 2. Diet intervention (low GI diet) vs standard/other care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Excessive weight gain	2	833	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.55, 0.99]
1.1 Low risk population	1	317	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.38, 0.94]
1.2 High risk population	2	516	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.61, 1.08]
2 Weight gain (kg)	5		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Mixed risk population	3		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 High risk population	2		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Low weight gain	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 High risk population	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Preterm birth	2	804	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.11, 1.02]
4.1 Mixed risk population	1	759	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.10, 1.46]
4.2 High risk population	1	45	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.03, 1.81]
5 Caesarean delivery	2	133	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.33, 3.01]
5.1 High risk population	2	133	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.33, 3.01]
6 Macrosomia (Infant birthweight > 4000 g)	4	1472	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.77, 1.20]
6.1 Mixed risk population	2	1335	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.75, 1.17]
6.2 High risk population	2	137	Risk Ratio (M-H, Random, 95% CI)	2.47 [0.68, 8.95]

Comparison 3. Diet and exercise counselling vs standard/other care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Excessive weight gain	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Low risk population	2	247	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.55, 0.95]
1.2 Mixed risk population	1	219	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.83, 1.15]
1.3 High risk women	9	2725	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.71, 1.02]
2 Weight gain (kg)	13		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Low risk population	2	241	Mean Difference (IV, Random, 95% CI)	-0.92 [-2.12, 0.29]
2.2 Mixed risk population	3	444	Mean Difference (IV, Random, 95% CI)	-1.80 [-3.36, -0.24]
2.3 High risk women	11	2741	Mean Difference (IV, Random, 95% CI)	-0.71 [-1.34, -0.08]
3 Low weight gain	5	2552	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.89, 1.72]
3.1 Low risk population	2	247	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.74, 2.39]
3.2 High risk women	5	2305	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.79, 1.85]
4 Preterm birth	7	3170	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.57, 1.55]
4.1 Low risk population	2	243	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.19, 5.09]
4.2 Mixed risk population	1	197	Risk Ratio (M-H, Random, 95% CI)	1.63 [0.84, 3.18]
4.3 High risk population	6	2730	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.43, 1.60]
5 Pre-eclampsia	7	3139	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.75, 1.34]
5.1 Low risk population	2	243	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.10, 1.22]
5.2 High risk women	7	2896	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.79, 1.43]
6 Caesarean delivery	9	3406	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.80, 1.00]
6.1 Low risk population	2	243	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.59, 1.48]
6.2 Mixed risk population	2	310	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.41, 1.05]

6.3 High risk women	7	2853	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.76, 1.04]
7 Macrosomia (Infant birthweight > 4000 g)	10	3705	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.77, 1.11]
7.1 Low risk population	2	243	Risk Ratio (M-H, Random, 95% CI)	2.18 [0.63, 7.58]
7.2 Mixed risk population	1	210	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.75, 2.56]
7.3 High risk women	9	3252	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.73, 1.00]

Comparison 4. Exercise vs standard/other care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Excessive weight gain	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Low risk population	2	953	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.47, 1.02]
1.2 Mixed risk population	3	1592	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.66, 0.88]
1.3 High risk population	5	690	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.73, 0.95]
2 Weight gain (kg)	8		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Low risk population	1	687	Mean Difference (IV, Random, 95% CI)	-1.5 [-2.08, -0.92]
2.2 Mixed risk population	4	1196	Mean Difference (IV, Random, 95% CI)	-1.00 [-2.01, 0.01]
2.3 High risk women	5	548	Mean Difference (IV, Random, 95% CI)	-0.34 [-1.15, 0.47]
3 Low weight gain	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Low risk population	1	687	Risk Ratio (M-H, Random, 95% CI)	1.29 [1.06, 1.58]
3.2 Mixed risk population	2	1336	Risk Ratio (M-H, Random, 95% CI)	1.20 [1.00, 1.43]
3.3 High risk population	3	504	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.66, 1.60]
4 Preterm birth	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Low risk population	1	687	Risk Ratio (M-H, Random, 95% CI)	4.20 [0.90, 19.65]
4.2 Mixed risk population	3	1129	Risk Ratio (M-H, Random, 95% CI)	1.92 [0.75, 4.93]
4.3 High risk population	3	504	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.51, 3.55]
5 Pre-eclampsia	4	1253	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.58, 1.66]
5.1 Mixed risk population	2	1024	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.52, 1.60]
5.2 High risk population	2	229	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.38, 6.73]
6 Caesarean delivery	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Low risk population	1	687	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.63, 1.21]
6.2 Mixed risk population	6	2263	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.76, 1.22]
6.3 High risk population	5	645	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.81, 1.20]
7 Macrosomia (Infant birthweight > 4000 g)	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Low risk population	1	687	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.26, 1.41]
7.2 Mixed risk population	7	2445	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.64, 1.02]
7.3 High risk population	3	504	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.22, 1.91]

Comparison 5. Diet and supervised exercise vs standard/other care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Excessive weight gain	5	689	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.61, 0.92]
1.1 Low risk population	2	106	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.16, 1.71]
1.2 Mixed risk population	2	235	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.47, 0.88]
1.3 High risk women	2	348	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.66, 1.06]
2 Weight gain (kg)	3	348	Mean Difference (IV, Random, 95% CI)	-1.31 [-1.00, 0.37]
2.1 Low risk population	1	57	Mean Difference (IV, Random, 95% CI)	-3.33 [-5.45, -1.21]
2.2 Mixed risk population	2	235	Mean Difference (IV, Random, 95% CI)	-0.88 [-2.40, 0.64]
2.3 High risk women	1	56	Mean Difference (IV, Random, 95% CI)	0.82 [-1.00, 4.64]
3 Low weight gain	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Mixed risk population	1	49	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.40, 5.50]
4 Pre-eclampsia	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 High risk women	1	304	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.51, 1.40]
5 Caesarean delivery	3	607	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.69, 1.45]
5.1 Low risk	1	57	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Mixed risk population	1	190	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.10, 3.36]
5.3 High risk women	2	360	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.48, 1.96]
6 Macrosomia (Infant birthweight > 4000 g)	3	398	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.71, 1.46]
6.1 Mixed risk population	2	94	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.23, 2.35]
6.2 High risk women	1	304	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.72, 1.54]

Comparison 6. Diet counselling/other vs standard/other care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Excessive weight gain	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Mixed risk population	3	443	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.08, 2.85]
1.2 High risk population	1	84	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.53, 1.62]
2 Weight gain (kg)	7		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Mixed risk population	3		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 High risk population	5		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Low weight gain	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Mixed risk population	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Preterm birth	3	591	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.26, 1.73]
4.1 Mixed risk population	1	235	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.15, 2.93]
4.2 High risk population	2	356	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.19, 2.32]
5 Pre-eclampsia	4	634	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.54, 1.48]
5.1 Mixed risk population	1	235	Risk Ratio (M-H, Random, 95% CI)	2.69 [0.55, 13.03]
5.2 High risk population	3	399	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.47, 1.35]
6 Caesarean delivery	5	754	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.93, 1.21]
6.1 Mixed risk population	2	355	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.60, 1.54]
6.2 High risk population	3	399	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.96, 1.27]

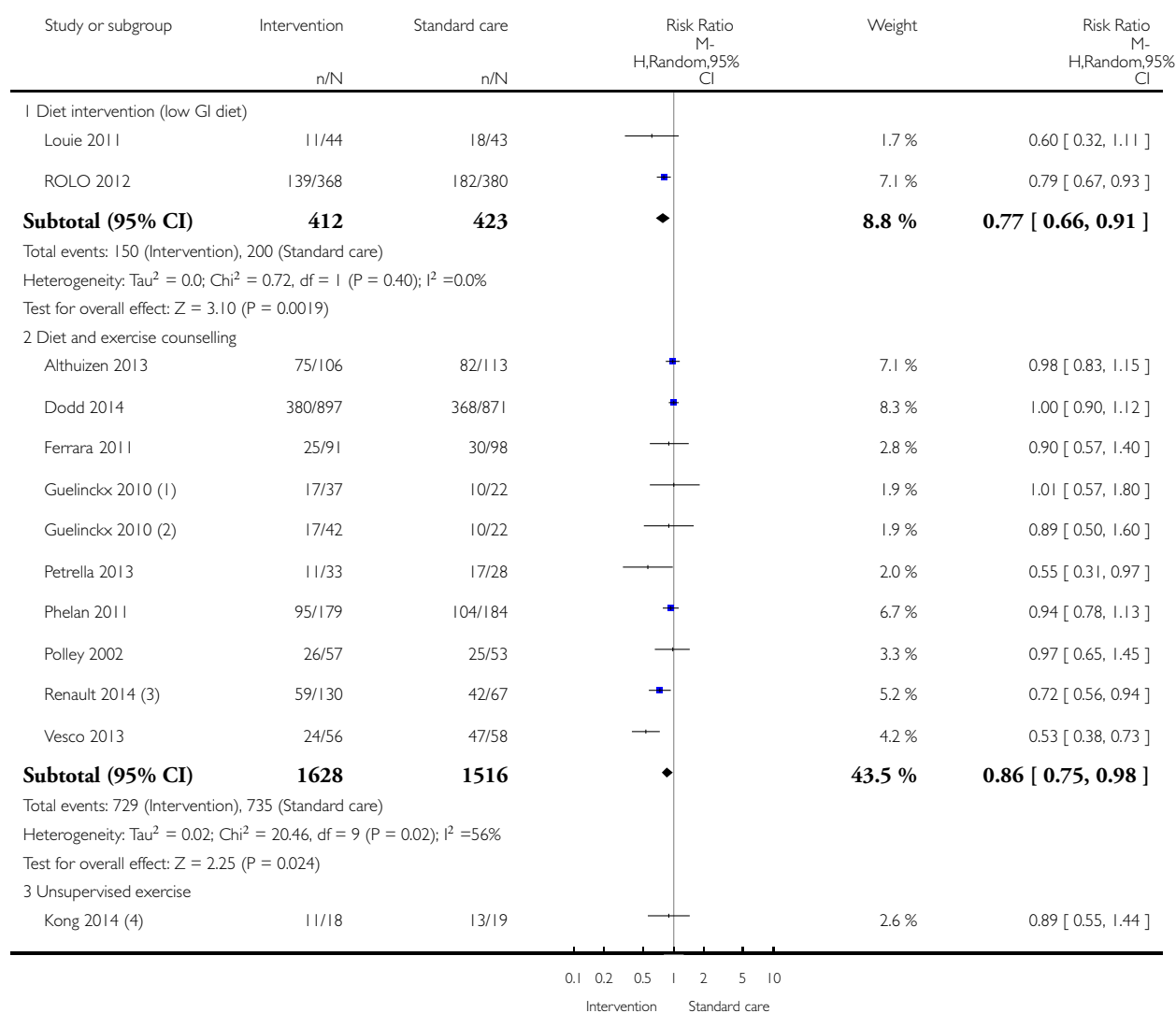
7 Macrosomia (Infant birthweight > 4000 g)	2	349	Risk Ratio (M-H, Random, 95% CI)	1.81 [0.88, 3.72]
7.1 High risk population	2	349	Risk Ratio (M-H, Random, 95% CI)	1.81 [0.88, 3.72]

Analysis 1.1. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 1 Excessive weight gain.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

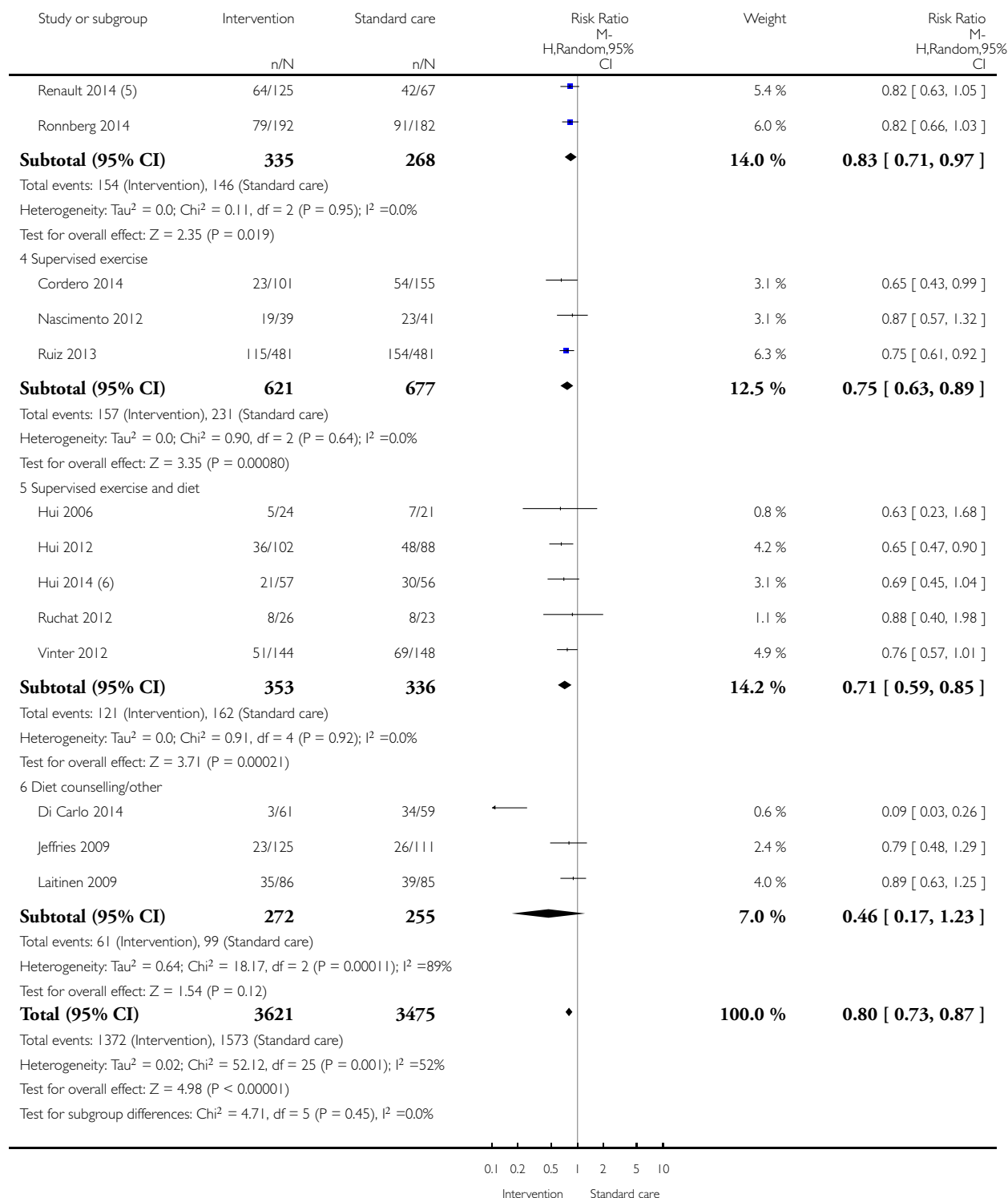
Comparison: 1 All diet and/or exercise interventions vs standard/other care

Outcome: 1 Excessive weight gain



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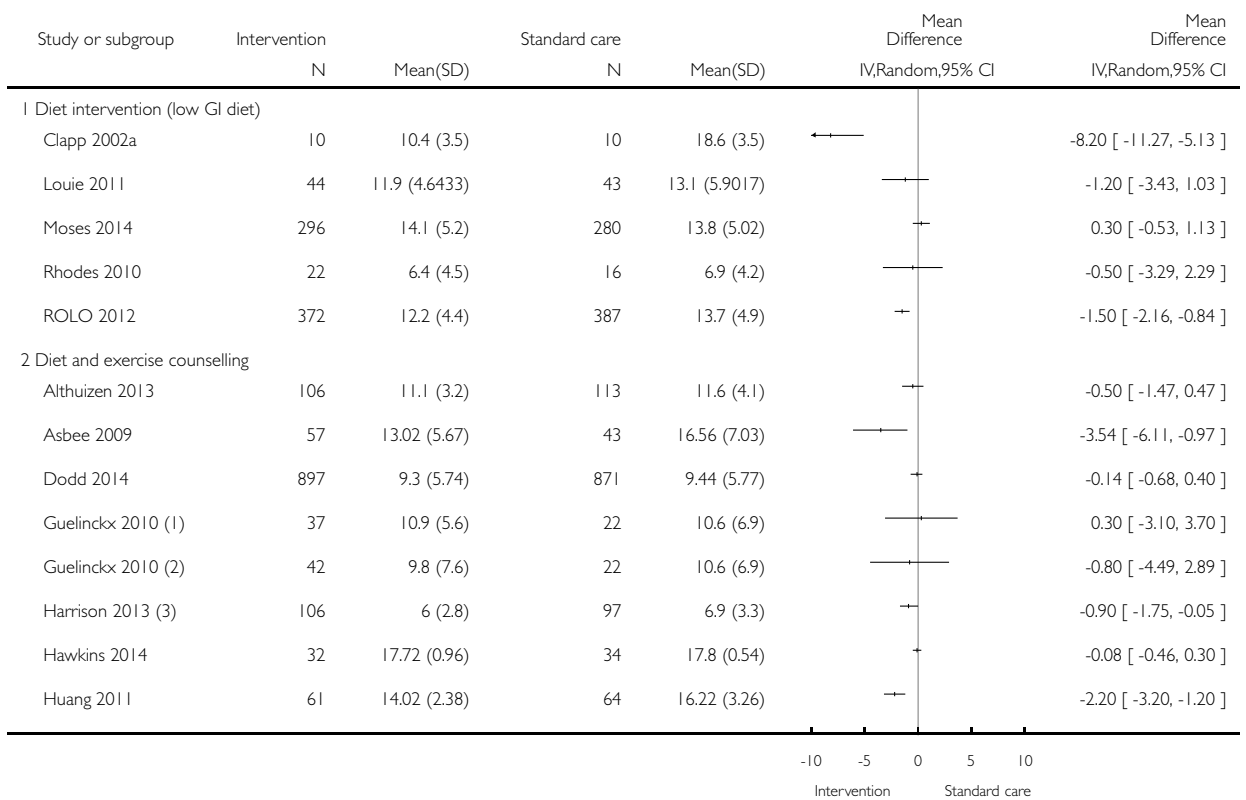
- (1) 3-arm: control group halved (brochure only arm)
- (2) 3-arm: control group halved (diet counselling plus brochure arm)
- (3) 3-arms: control group halved
- (4) Reported results stratified by risk/BMI
- (5) 3-arms: control group halved
- (6) Reported results stratified by risk/BMI

Analysis 1.2. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 2 Weight gain (kg).

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

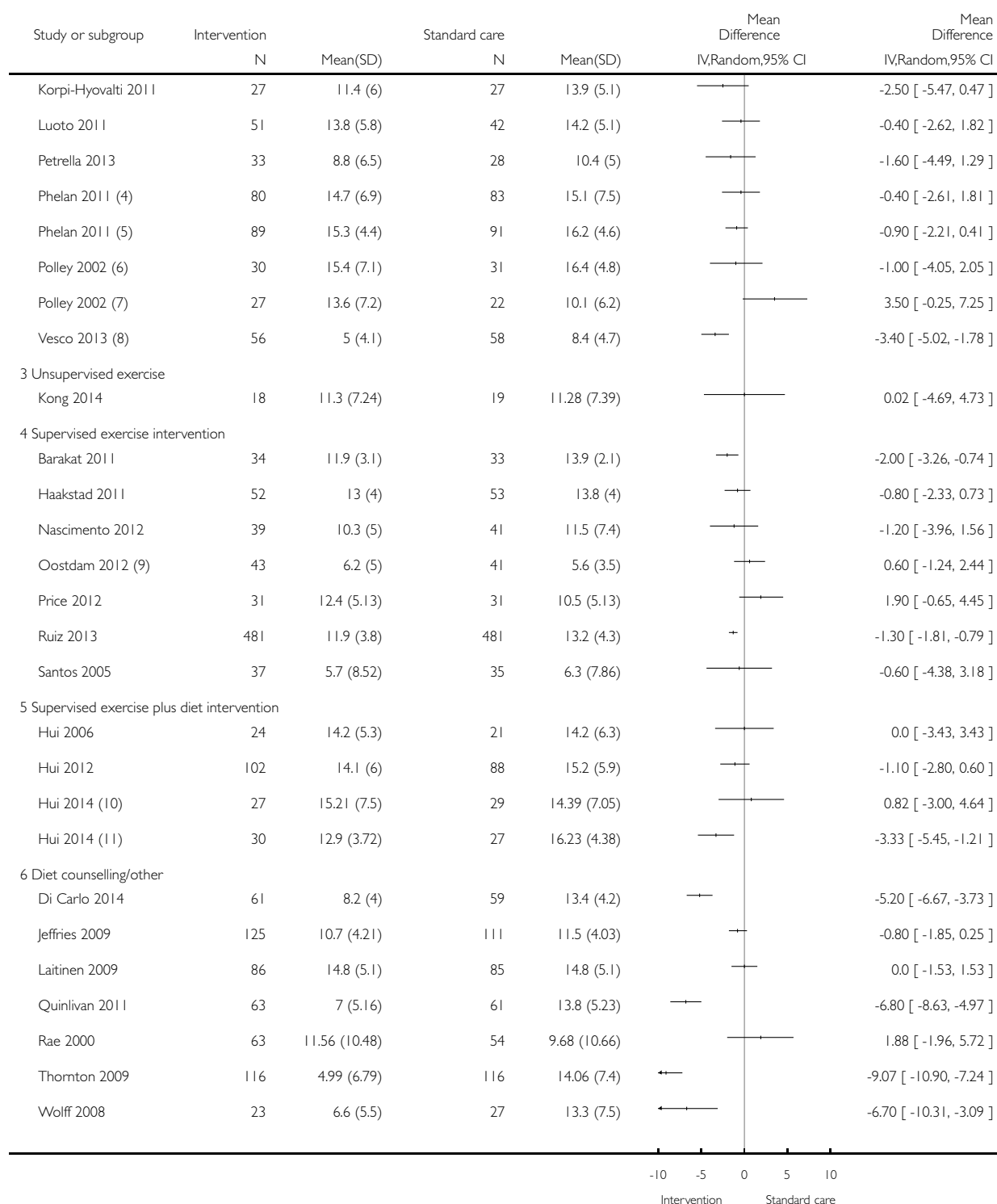
Comparison: 1 All diet and/or exercise interventions vs standard/other care

Outcome: 2 Weight gain (kg)



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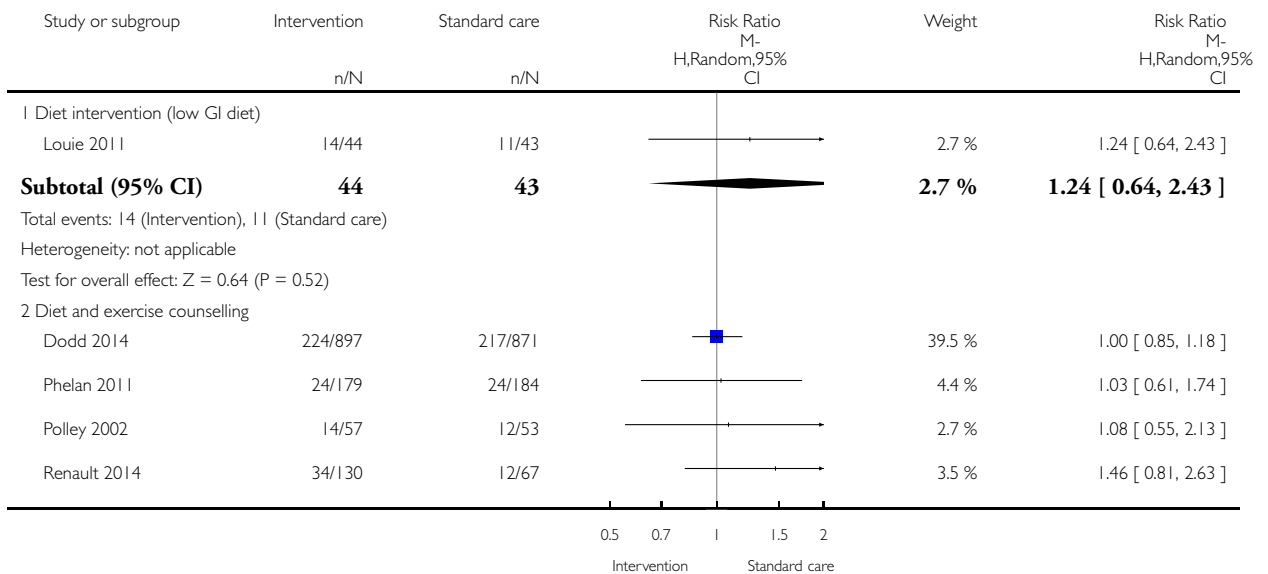
- (1) brochure only
- (2) diet counselling plus brochure
- (3) measured at 26-28 weeks
- (4) normal weight women
- (5) Overweight/obese women
- (6) Normal weight women
- (7) Overweight women
- (8) measured at 34 weeks
- (9) 31% missing data
- (10) BMI > 25 kg/m²
- (11) BMI < 25 kg/m²

Analysis 1.3. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 3 Low weight gain.

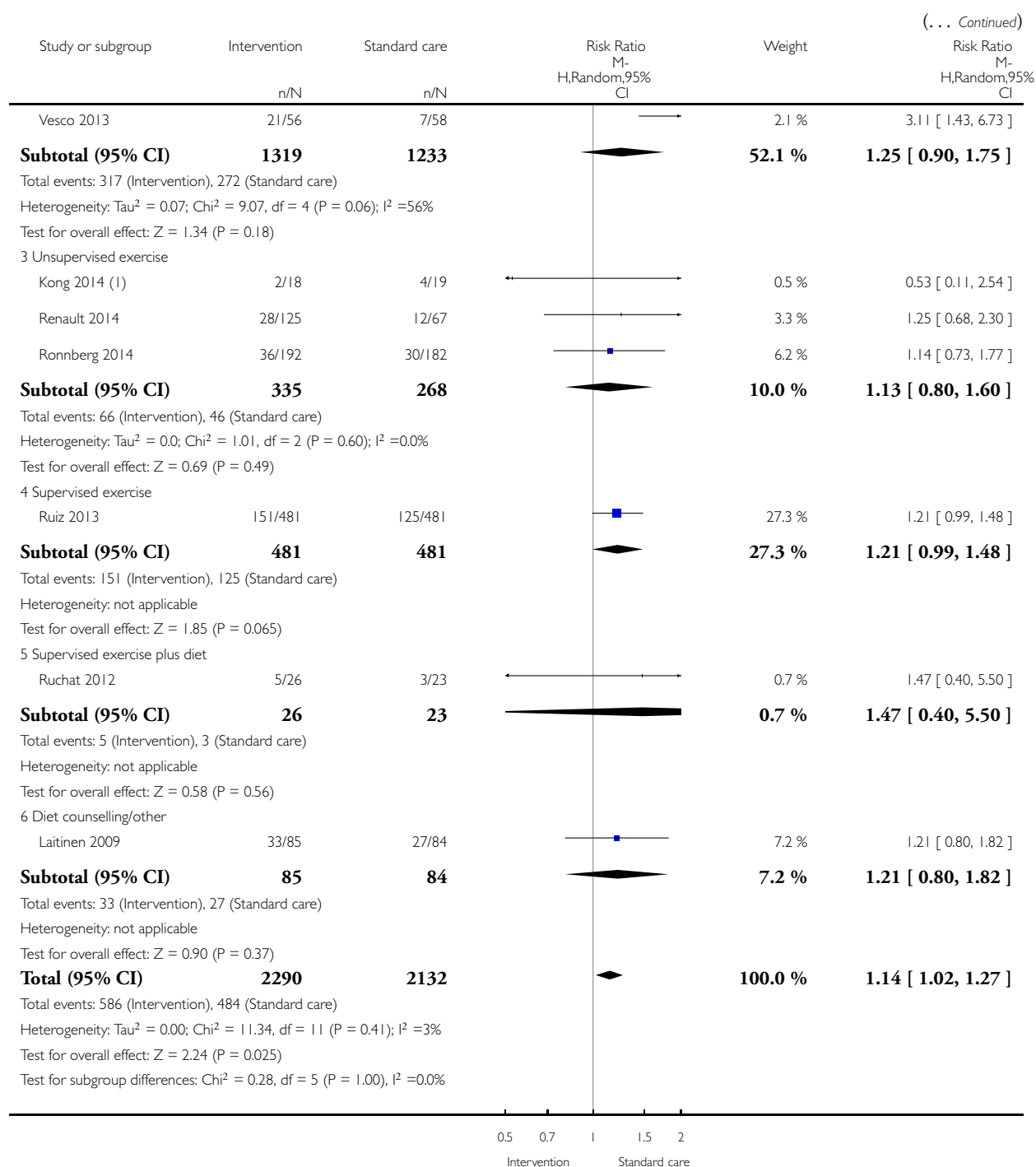
Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 1 All diet and/or exercise interventions vs standard/other care

Outcome: 3 Low weight gain



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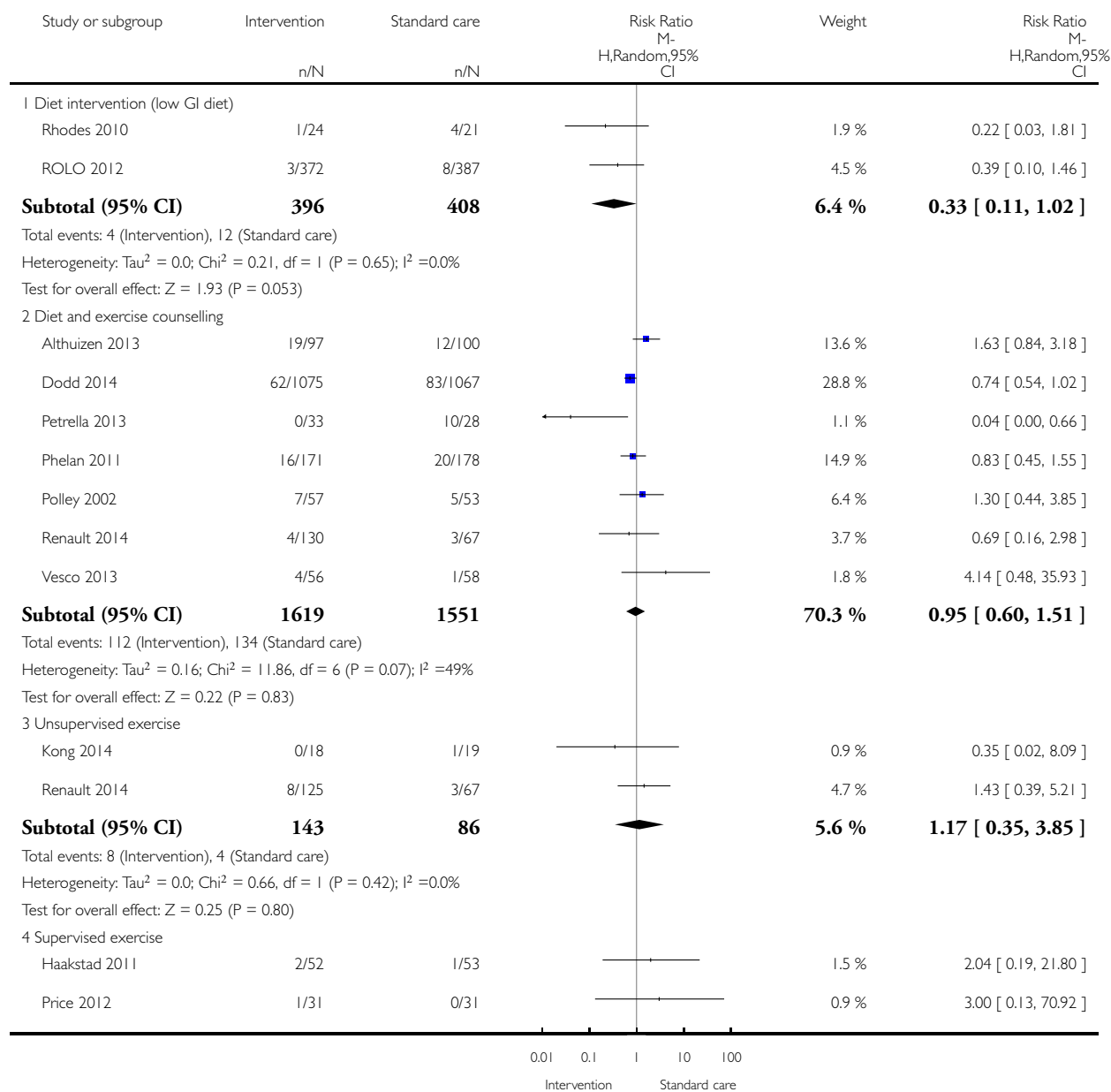
(1) combine overweight and obese women

Analysis 1.4. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 4 Preterm birth.

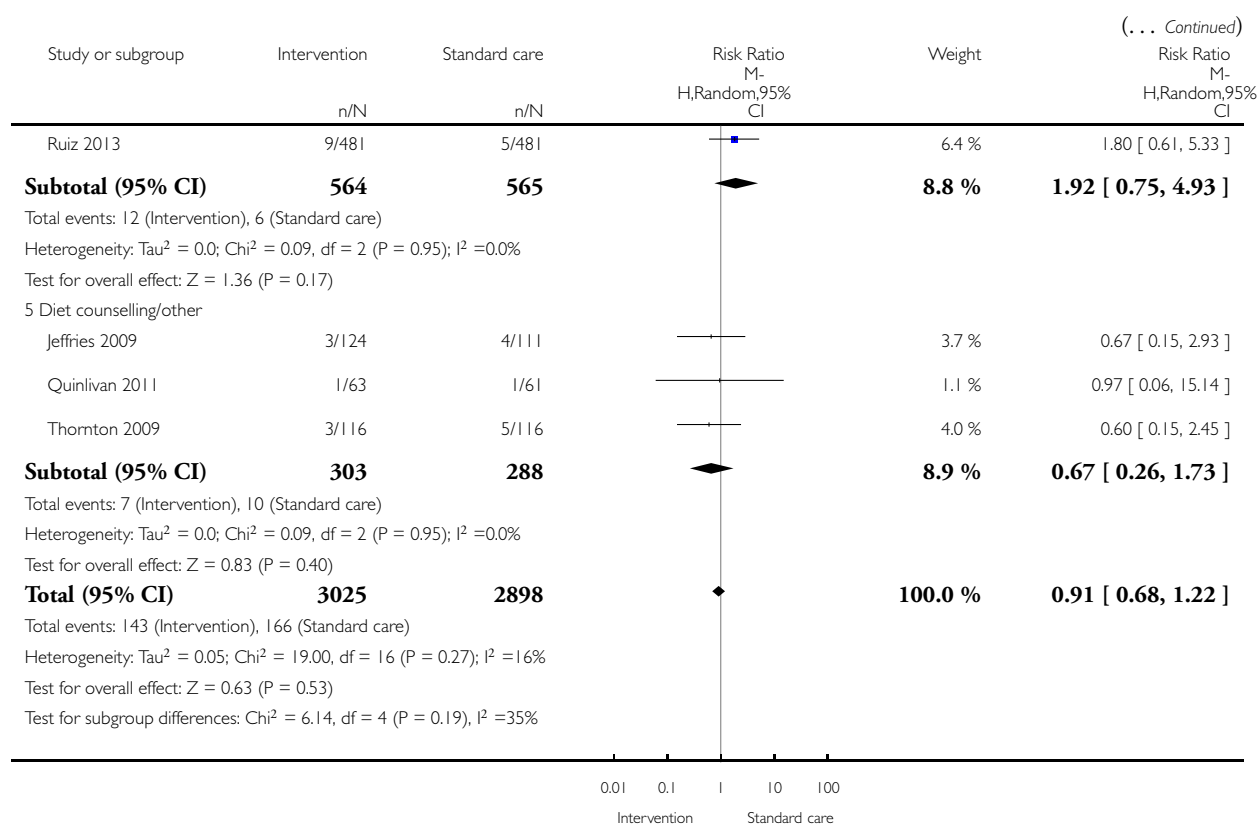
Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 1 All diet and/or exercise interventions vs standard/other care

Outcome: 4 Preterm birth



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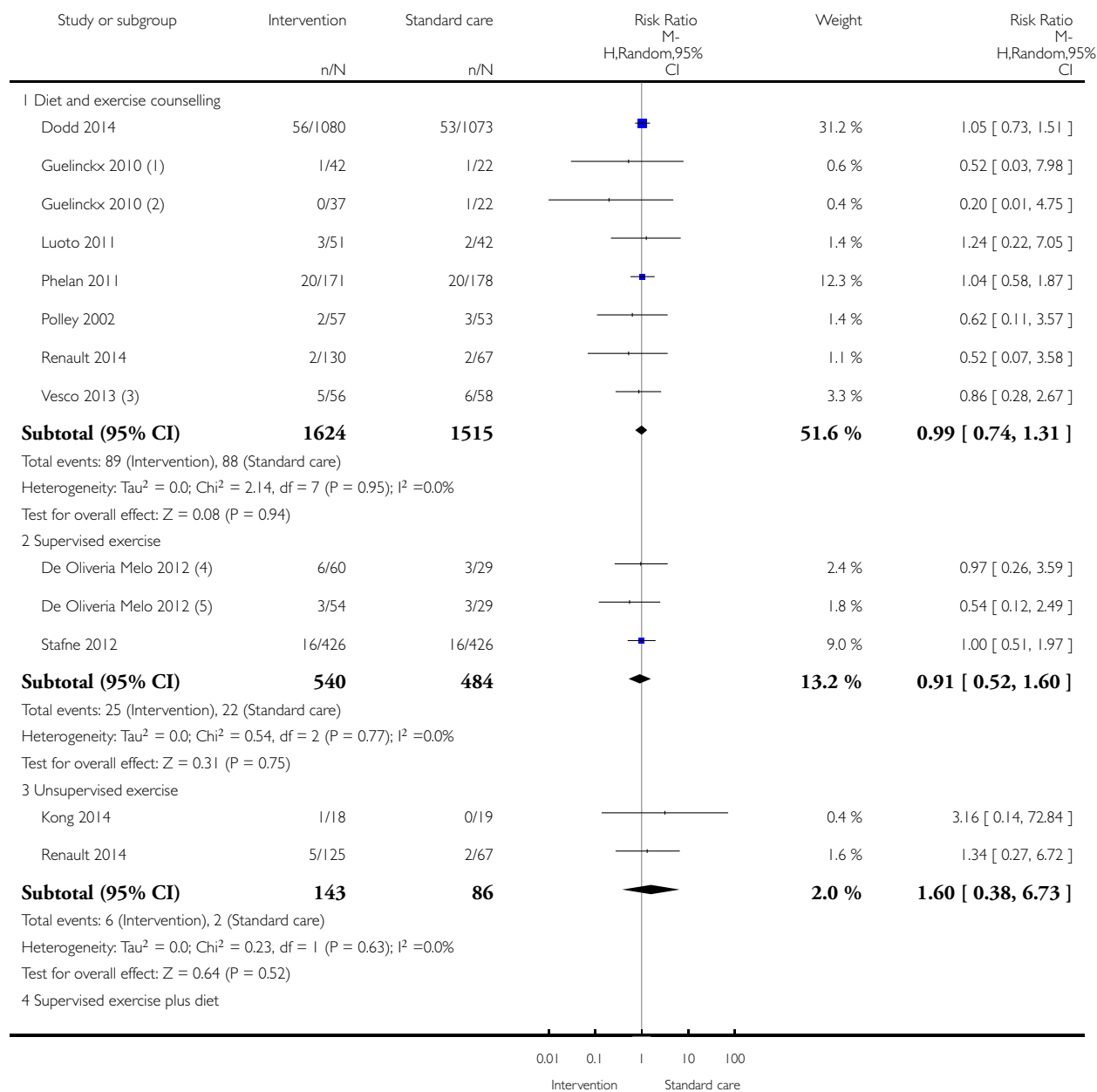


Analysis 1.5. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 5 Pre-eclampsia.

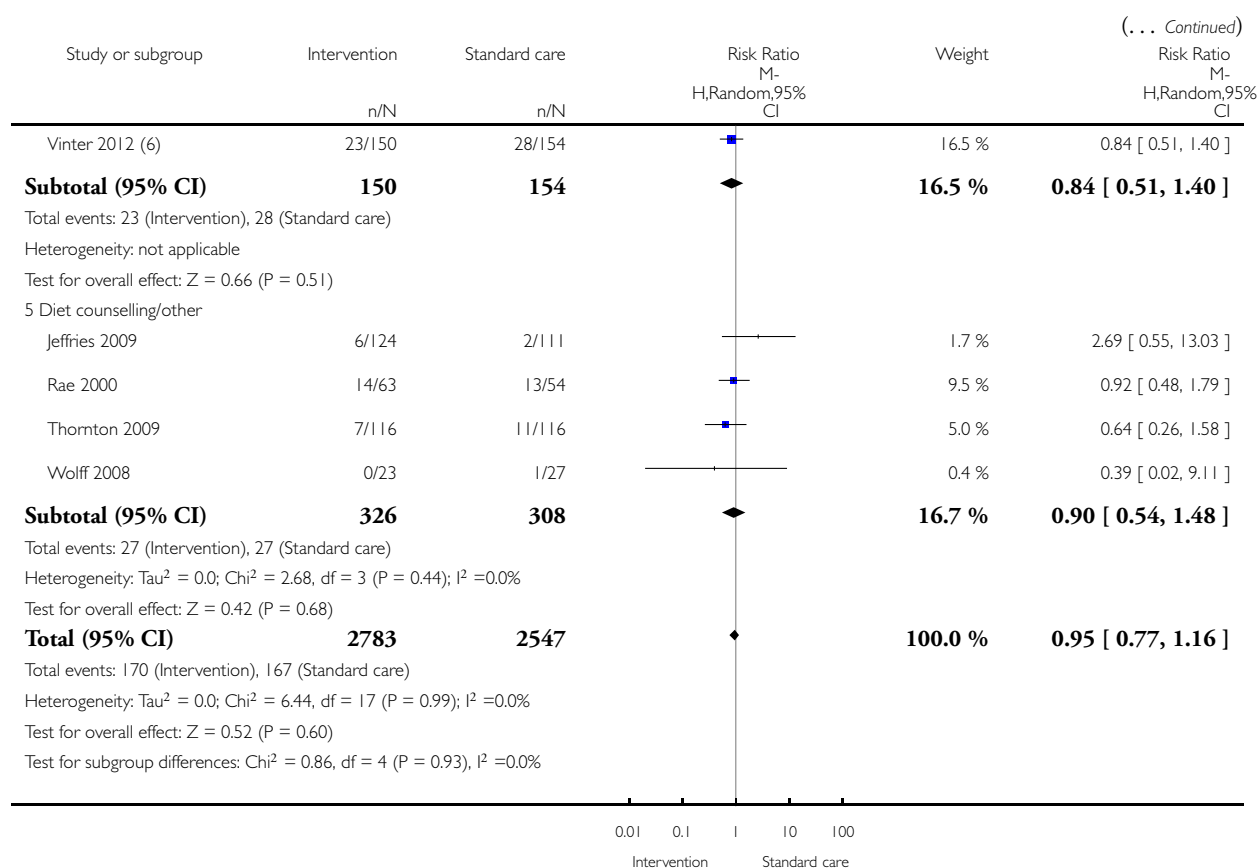
Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 1 All diet and/or exercise interventions vs standard/other care

Outcome: 5 Pre-eclampsia



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(1) Counselling and brochure

(2) Brochure only

(3) PE/PIH

(4) intervention from 20 weeks

(5) intervention from 13 weeks

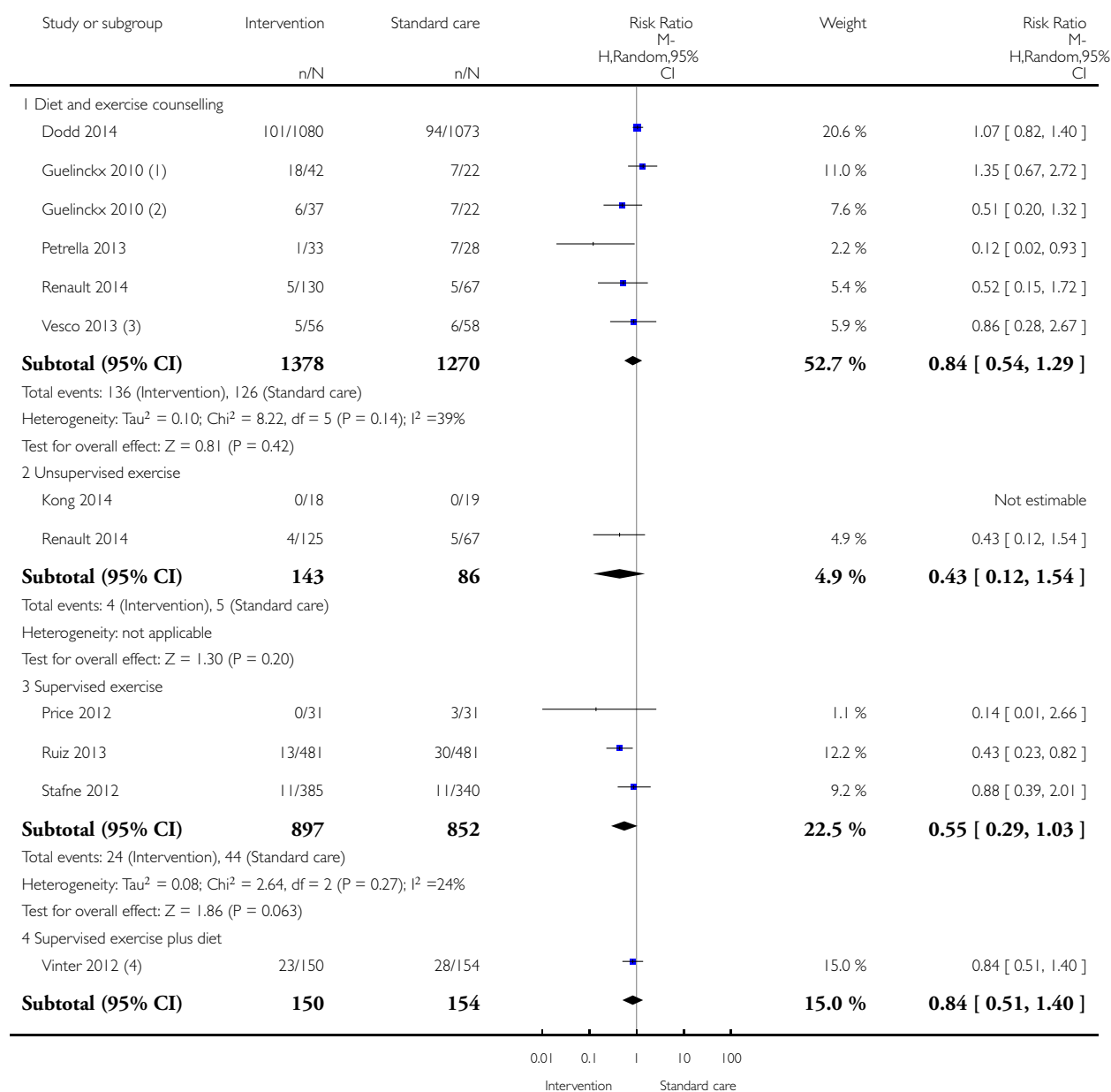
(6) Pre-eclampsia or pregnancy-induced hypertension

Analysis 1.6. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 6 Hypertension (not prespecified).

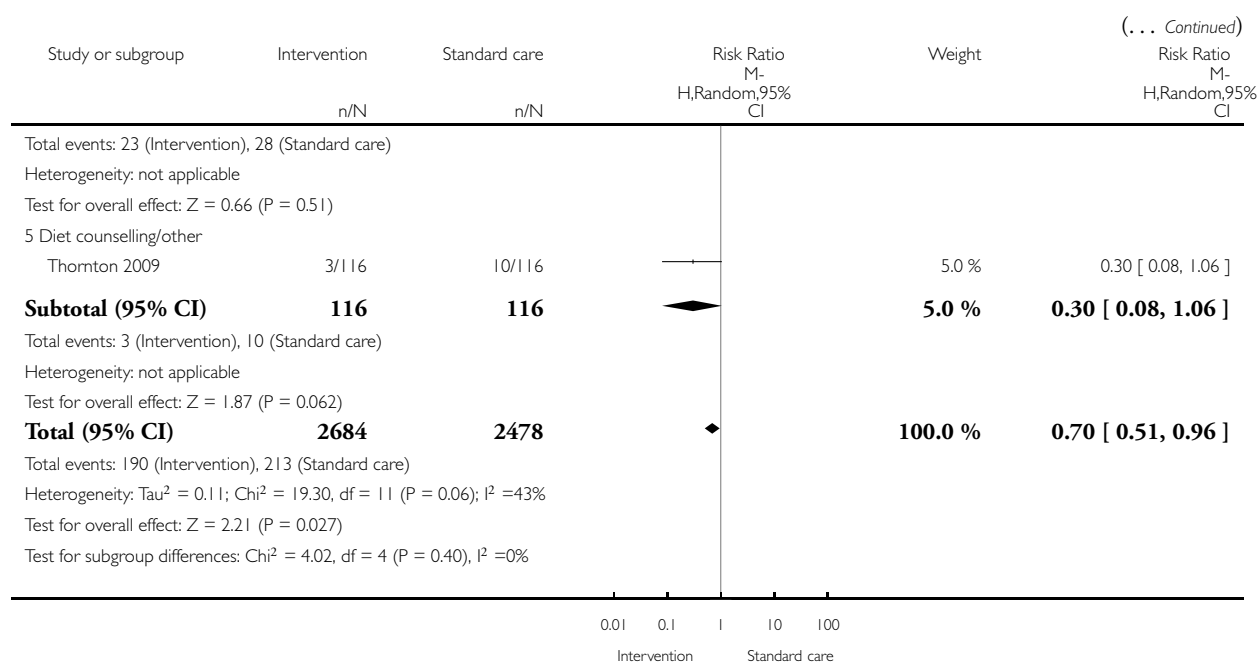
Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 1 All diet and/or exercise interventions vs standard/other care

Outcome: 6 Hypertension (not prespecified)



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(1) Brochure and counselling

(2) Brochure only

(3) PE/PIH

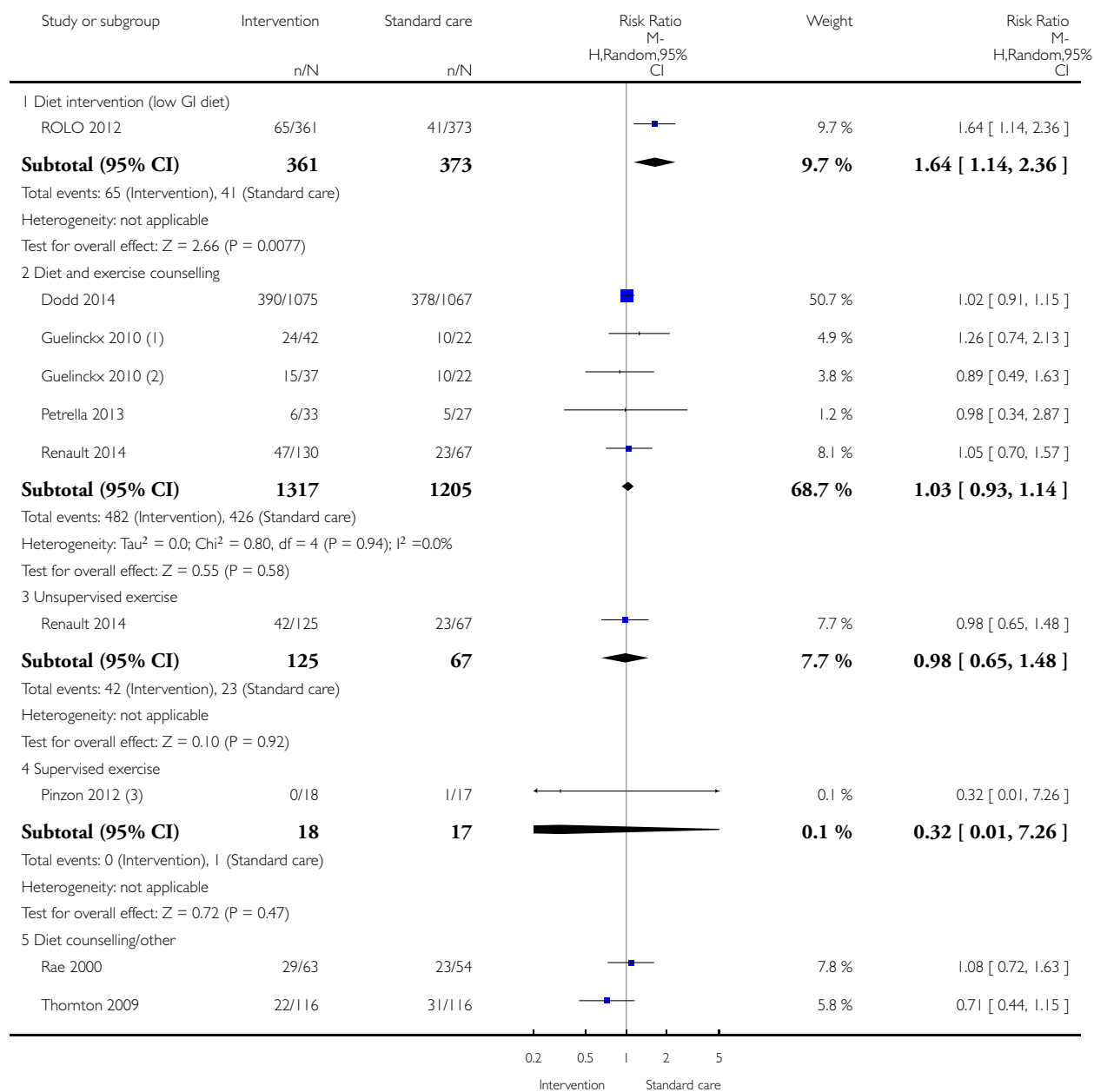
(4) Pre-eclampsia and pregnancy-induced hypertension

Analysis 1.7. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 7 Induction of labour.

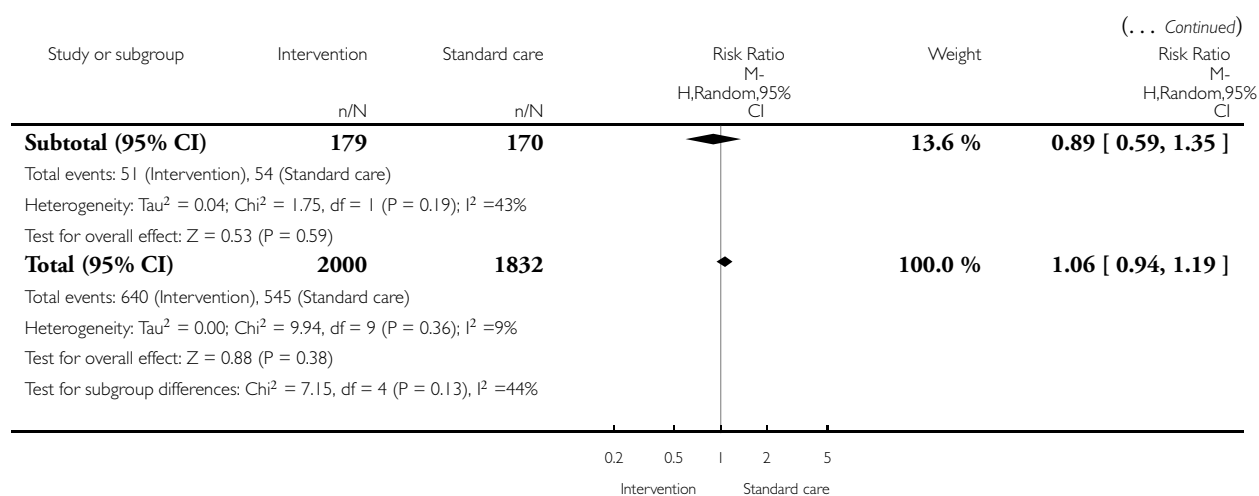
Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 1 All diet and/or exercise interventions vs standard/other care

Outcome: 7 Induction of labour



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(1) Counselling plus brochure

(2) Brochure only

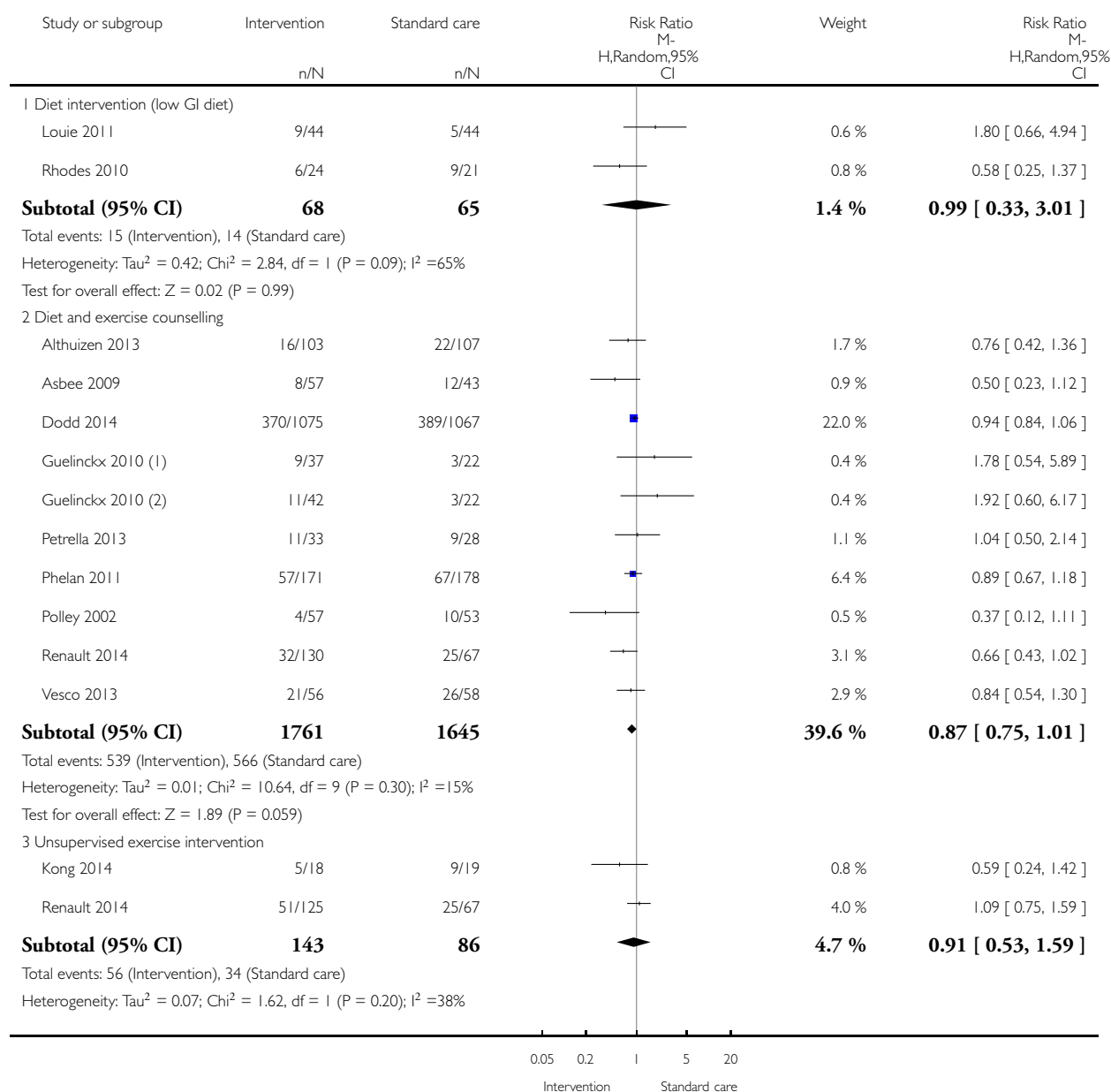
(3) 45% missing data

Analysis 1.8. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 8 Caesarean delivery.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

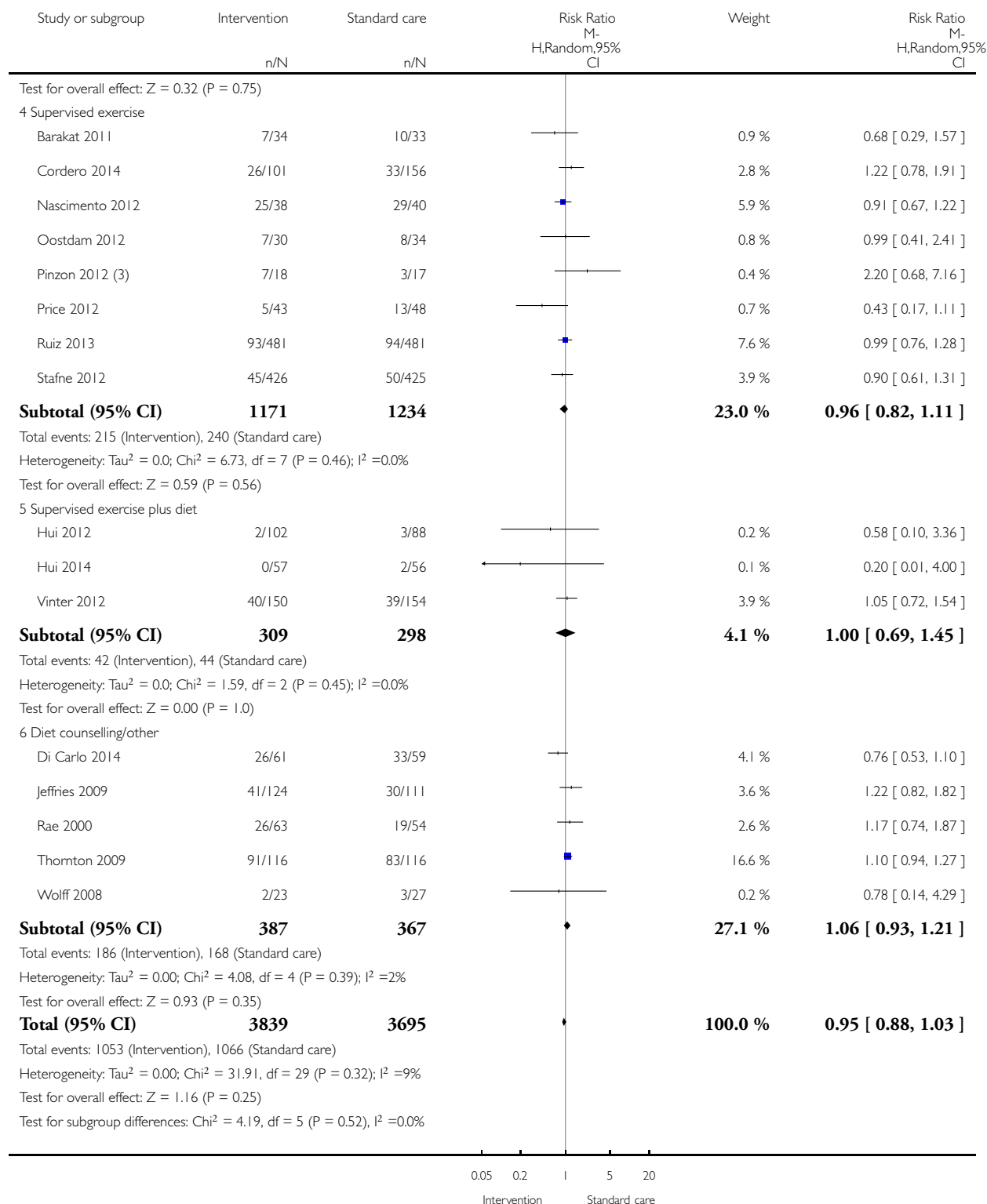
Comparison: 1 All diet and/or exercise interventions vs standard/other care

Outcome: 8 Caesarean delivery



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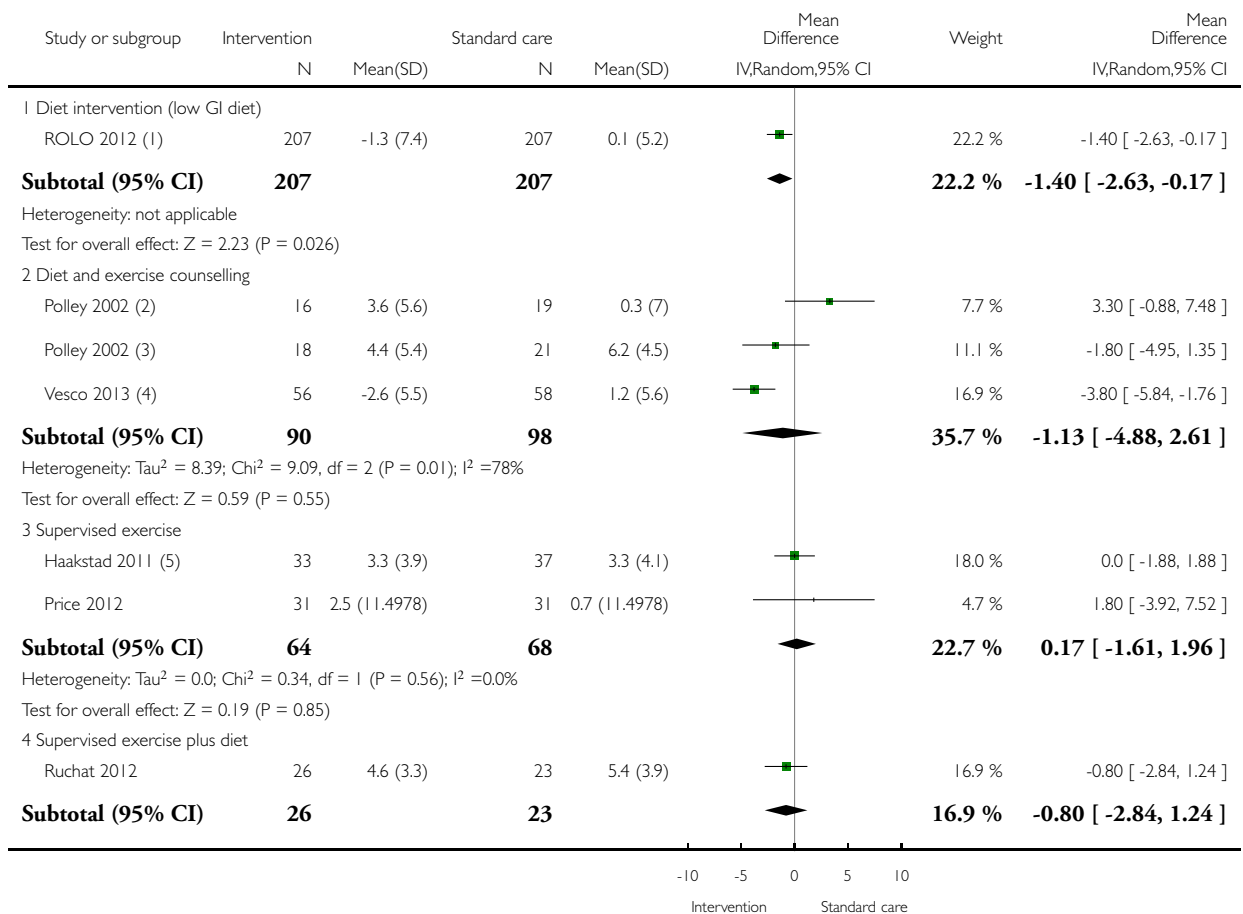
- (1) Brochure only
- (2) Counselling plus brochure
- (3) 45% missing data

Analysis 1.9. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 9 Postpartum weight retention (kg).

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

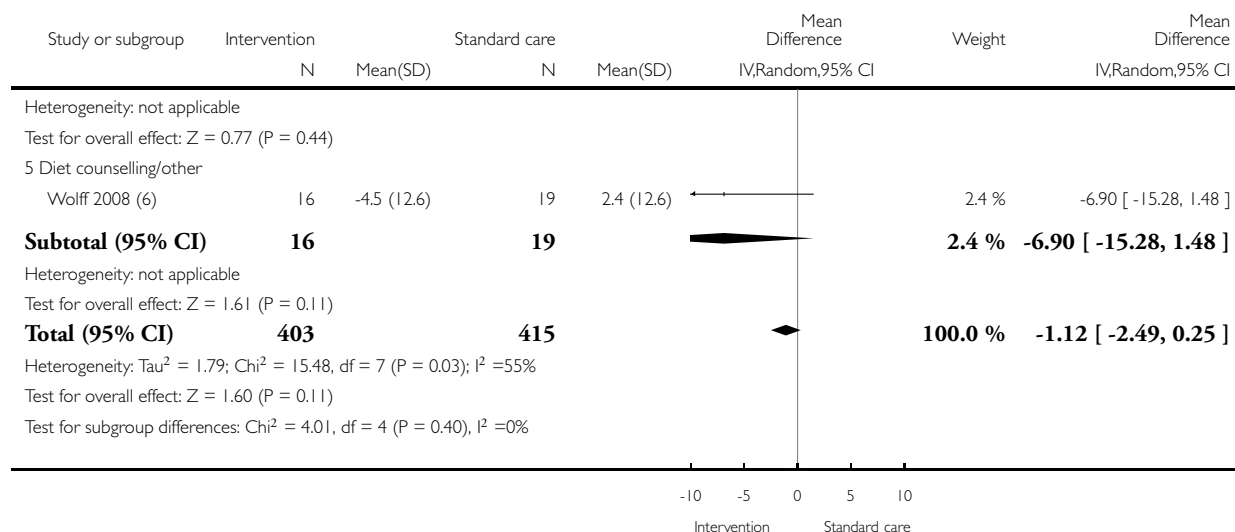
Comparison: 1 All diet and/or exercise interventions vs standard/other care

Outcome: 9 Postpartum weight retention (kg)



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(1) 3 months postpartum; self-reported and only 61.4% of participants responded

(2) overweight women (mean 8 weeks postpartum)

(3) normal weight women

(4) obese women (mean 3 weeks postpartum)

(5) missing data >30%

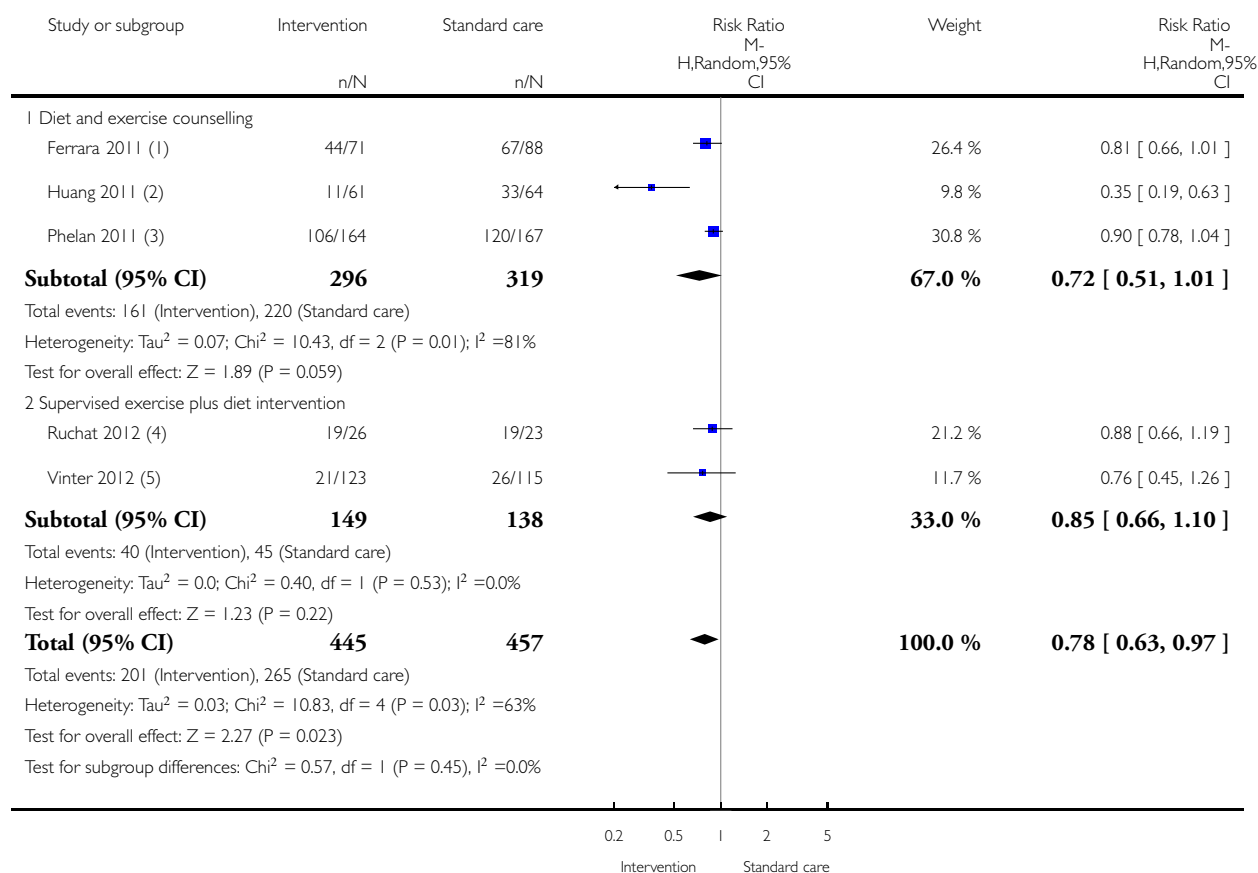
(6) obese women (mean 4 weeks postpartum)

Analysis 1.10. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 10 Postpartum weight retention (n/N; investigator defined time frame).

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 1 All diet and/or exercise interventions vs standard/other care

Outcome: 10 Postpartum weight retention (n/N; investigator defined time frame)



(1) 7 months postpartum; attrition >20%

(2) 6 months postpartum

(3) 1 year postpartum

(4) 2 months postpartum

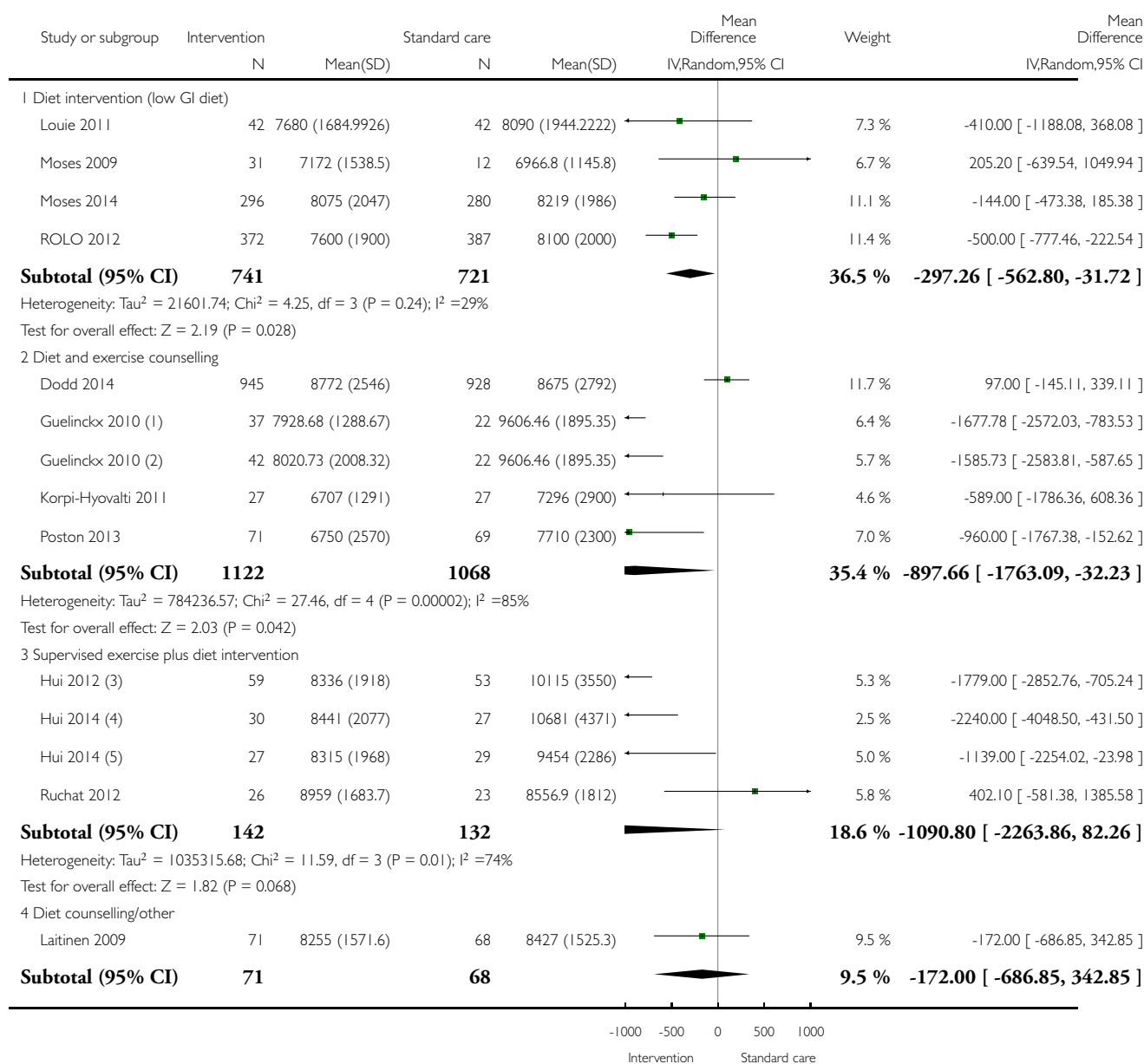
(5) 6 months postpartum

Analysis 1.11. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 11 Energy intake (kj).

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

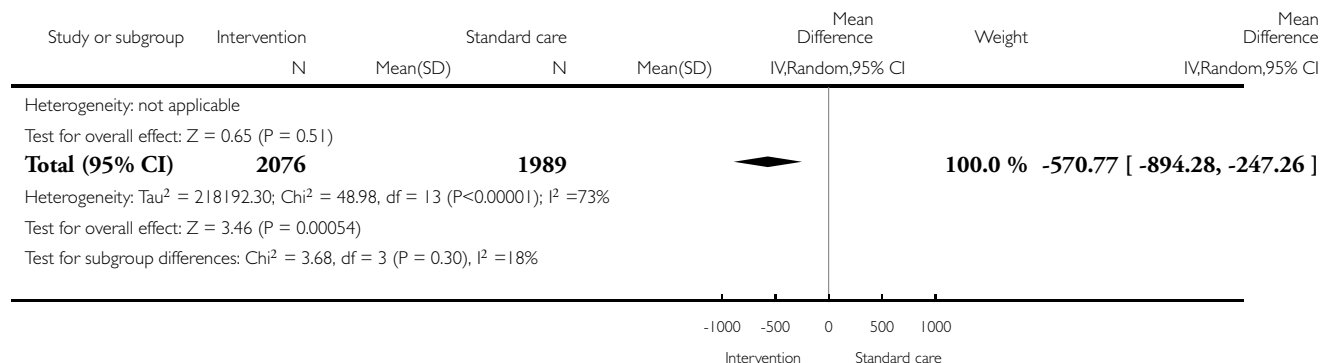
Comparison: 1 All diet and/or exercise interventions vs standard/other care

Outcome: 11 Energy intake (kj)



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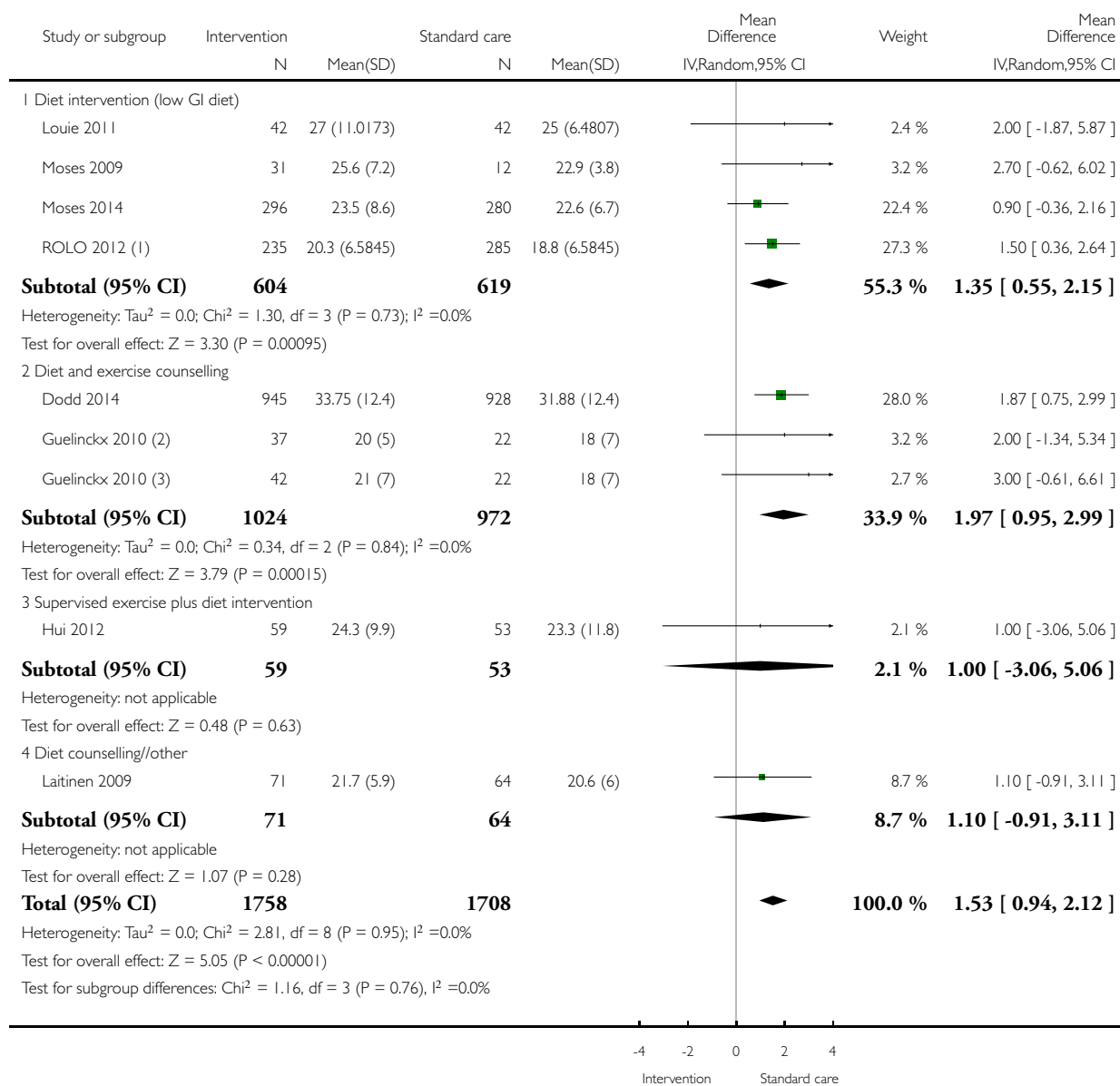
- (1) Brochure only
- (2) Counselling plus brochure
- (3) missing data >30%
- (4) BMI < 25 kg/m²
- (5) BMI > 25 kg/m²

Analysis 1.12. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 12 Fibre intake (g).

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 1 All diet and/or exercise interventions vs standard/other care

Outcome: 12 Fibre intake (g)



(1) missing data >30%

(2) Brochure only

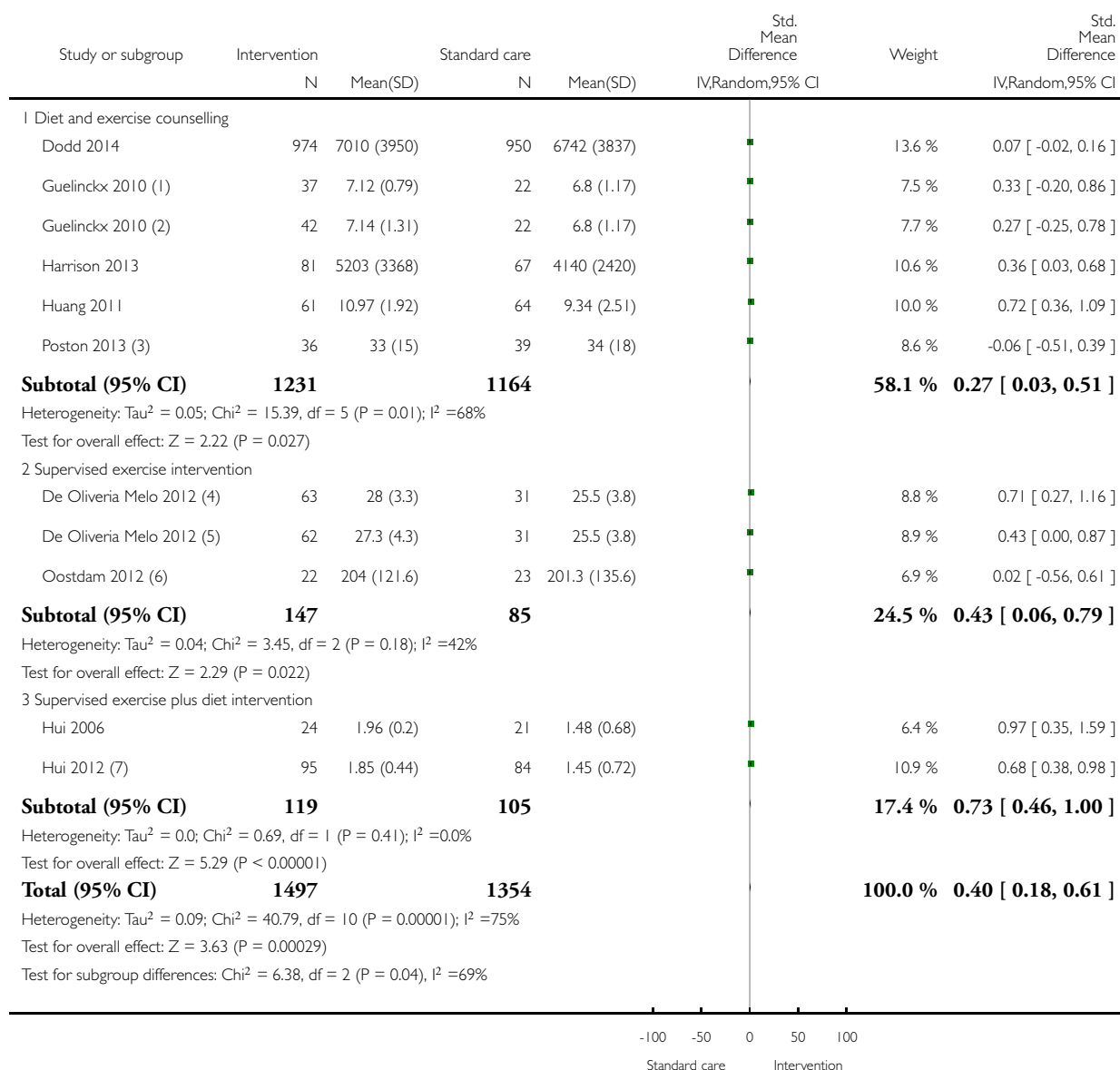
(3) Counselling plus brochure

Analysis 1.13. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 13 Physical activity score (26-29 weeks).

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 1 All diet and/or exercise interventions vs standard/other care

Outcome: 13 Physical activity score (26-29 weeks)



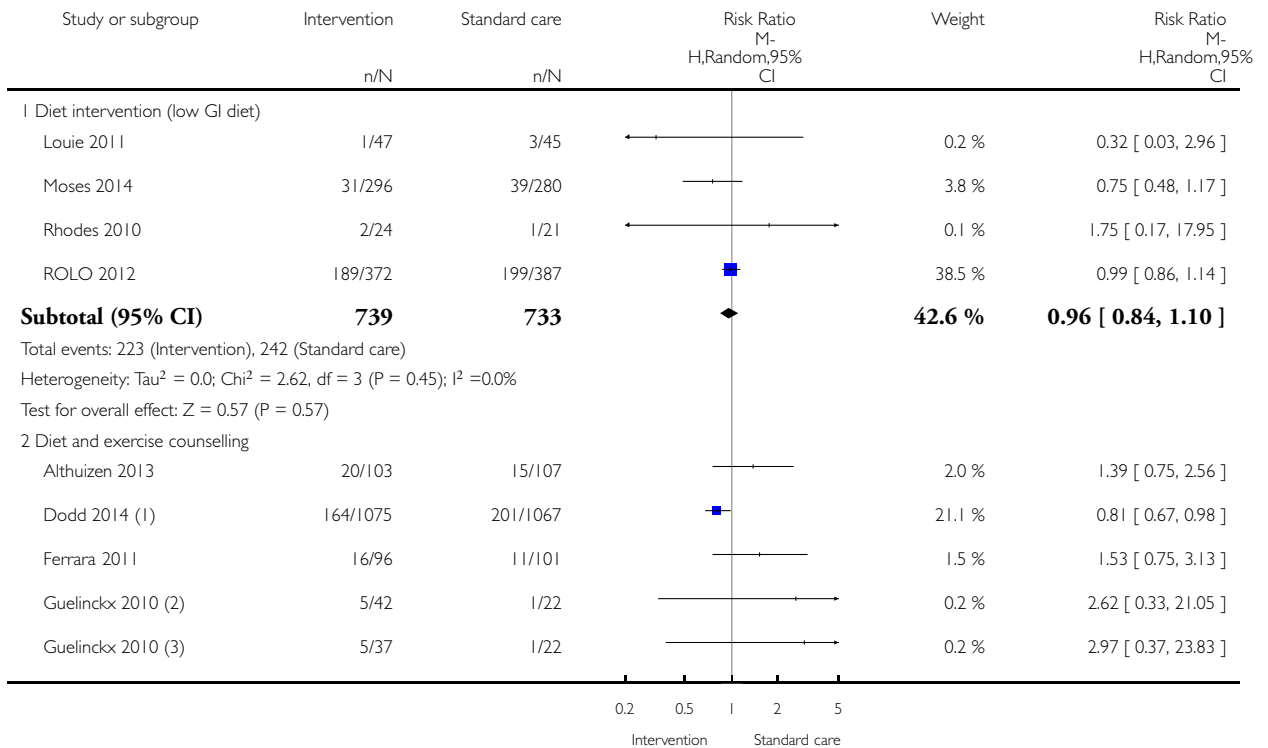
- (1) Brochure only
- (2) Counselling plus brochure
- (3) accelerometer min/day; missing data >50%
- (4) intervention from 20 weeks (VO2 max)
- (5) intervention from 13 weeks (VO2 max)
- (6) minutes per week; missing data >50%
- (7) physical activity index

Analysis 1.14. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 14 Macrosomia Infant birthweight > 4000 g.

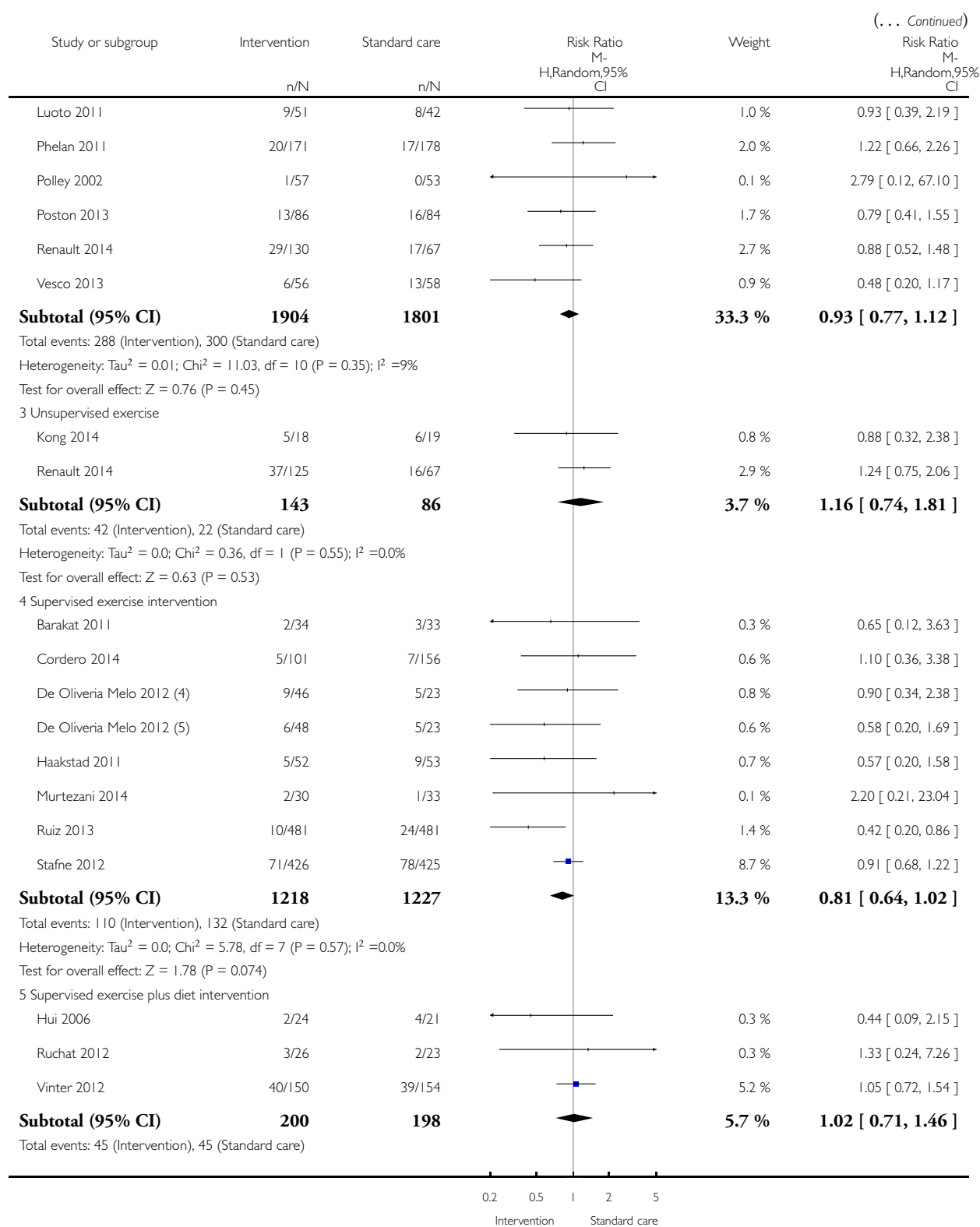
Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

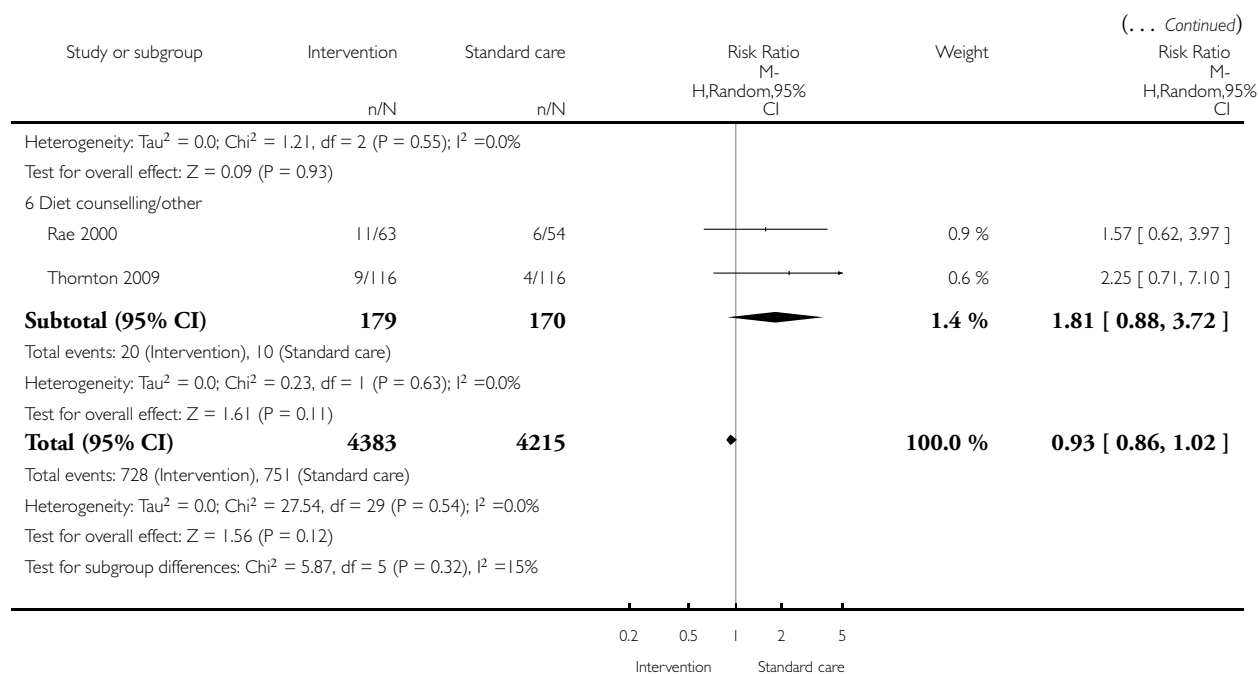
Comparison: 1 All diet and/or exercise interventions vs standard/other care

Outcome: 14 Macrosomia Infant birthweight > 4000 g



(Continued ...)





(1) 23 (2.1%) vs 39 (3.7%) had birthweight > 4.5 kg

(2) Counselling plus brochure

(3) Brochure only

(4) intervention from 13 weeks

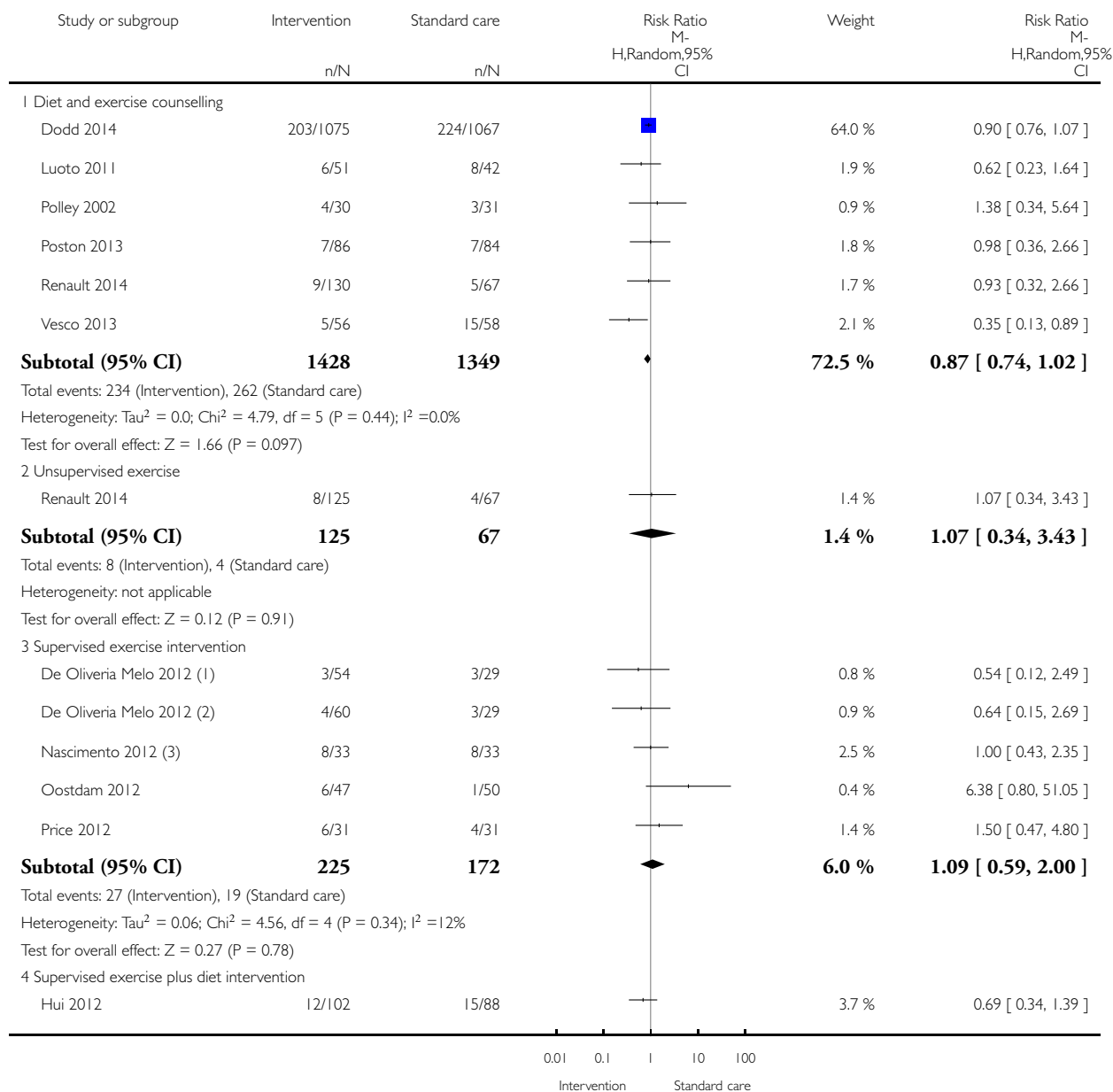
(5) intervention from 20 weeks

Analysis 1.15. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 15 Infant birthweight > 90th centile.

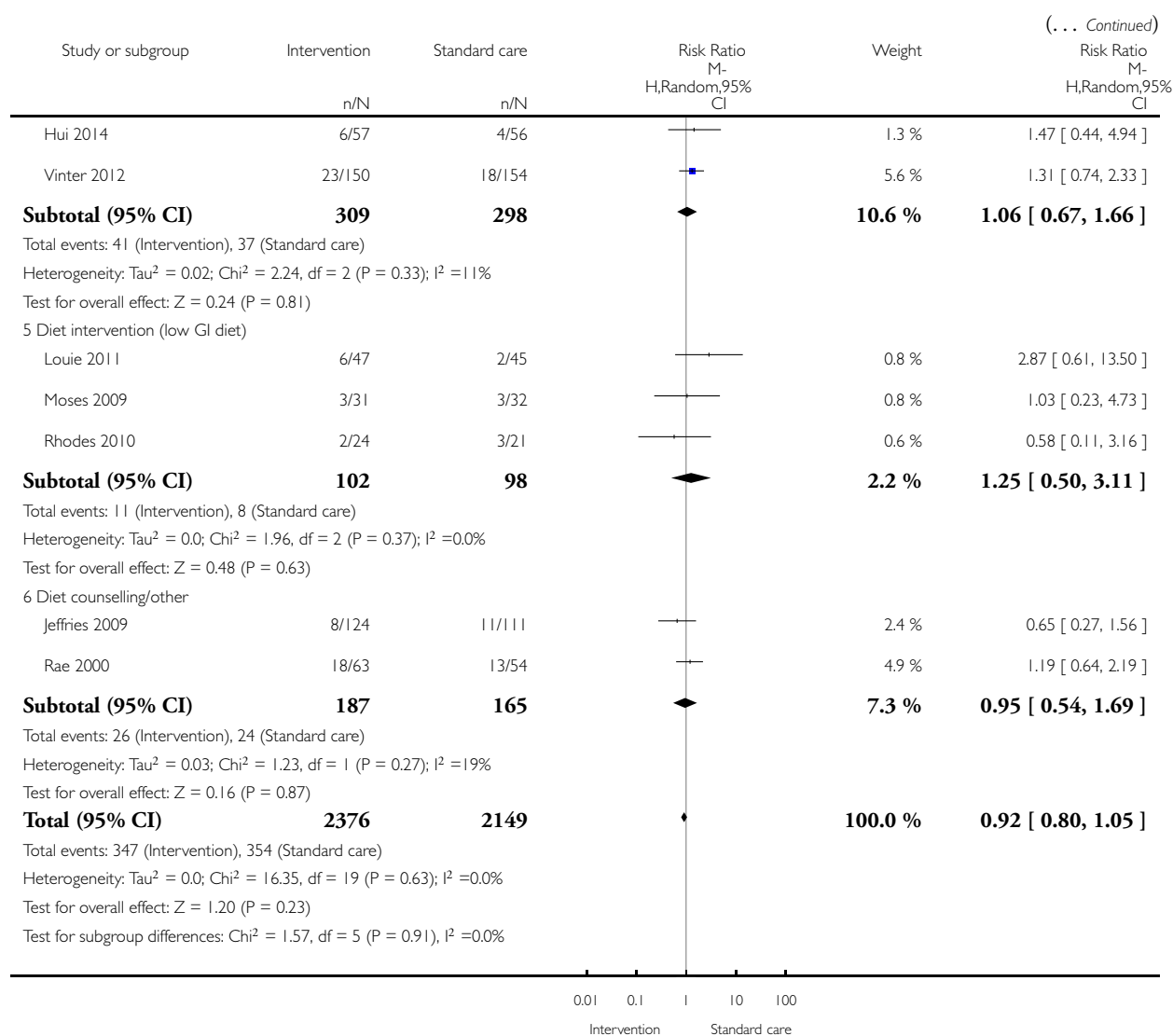
Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 1 All diet and/or exercise interventions vs standard/other care

Outcome: 15 Infant birthweight > 90th centile



(Continued ...)



(1) intervention from 13 weeks

(2) intervention from 20 weeks

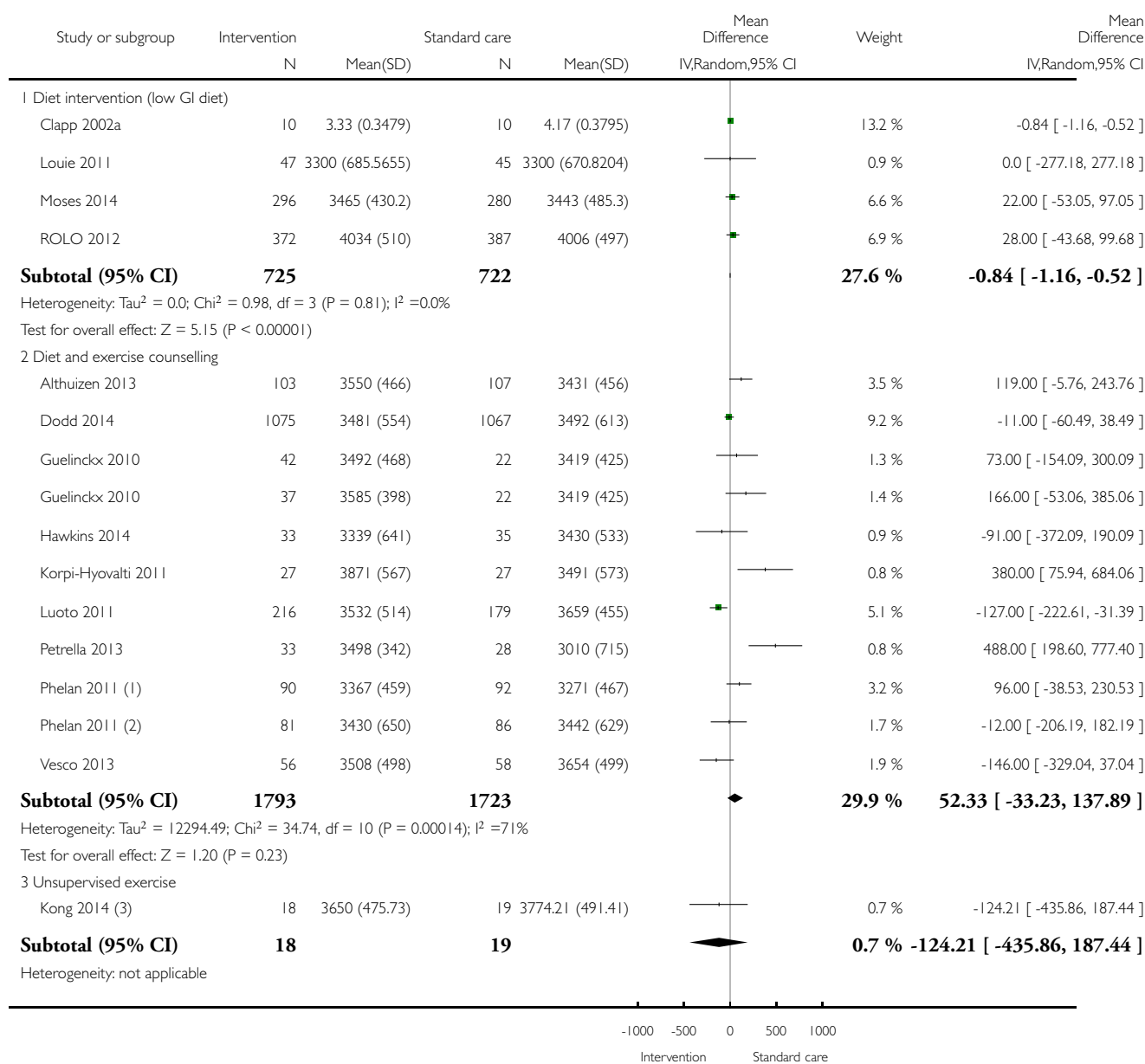
(3) missing data >20%

Analysis 1.16. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 16 Birthweight (g) (not prespecified).

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

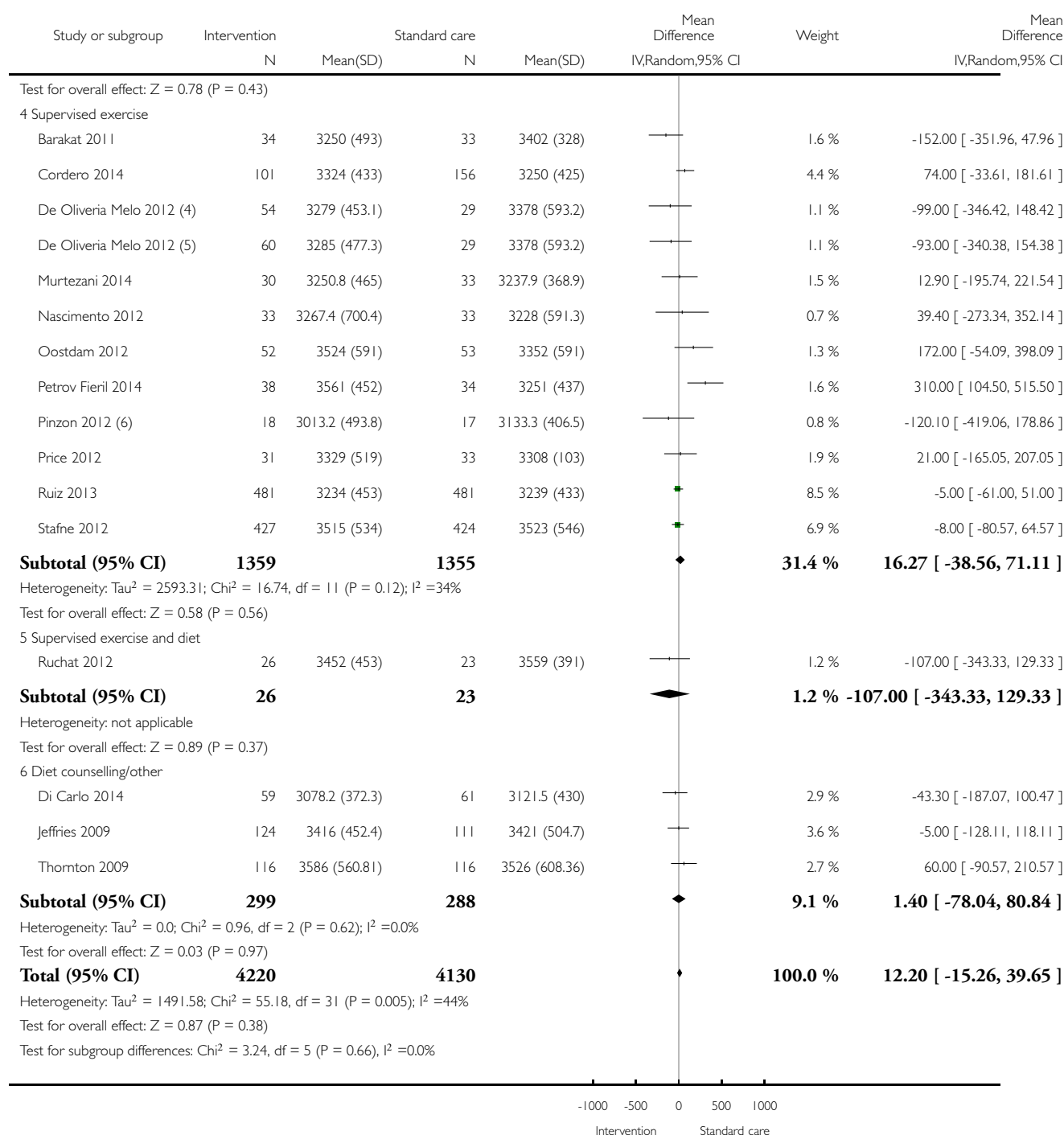
Comparison: 1 All diet and/or exercise interventions vs standard/other care

Outcome: 16 Birthweight (g) (not prespecified)



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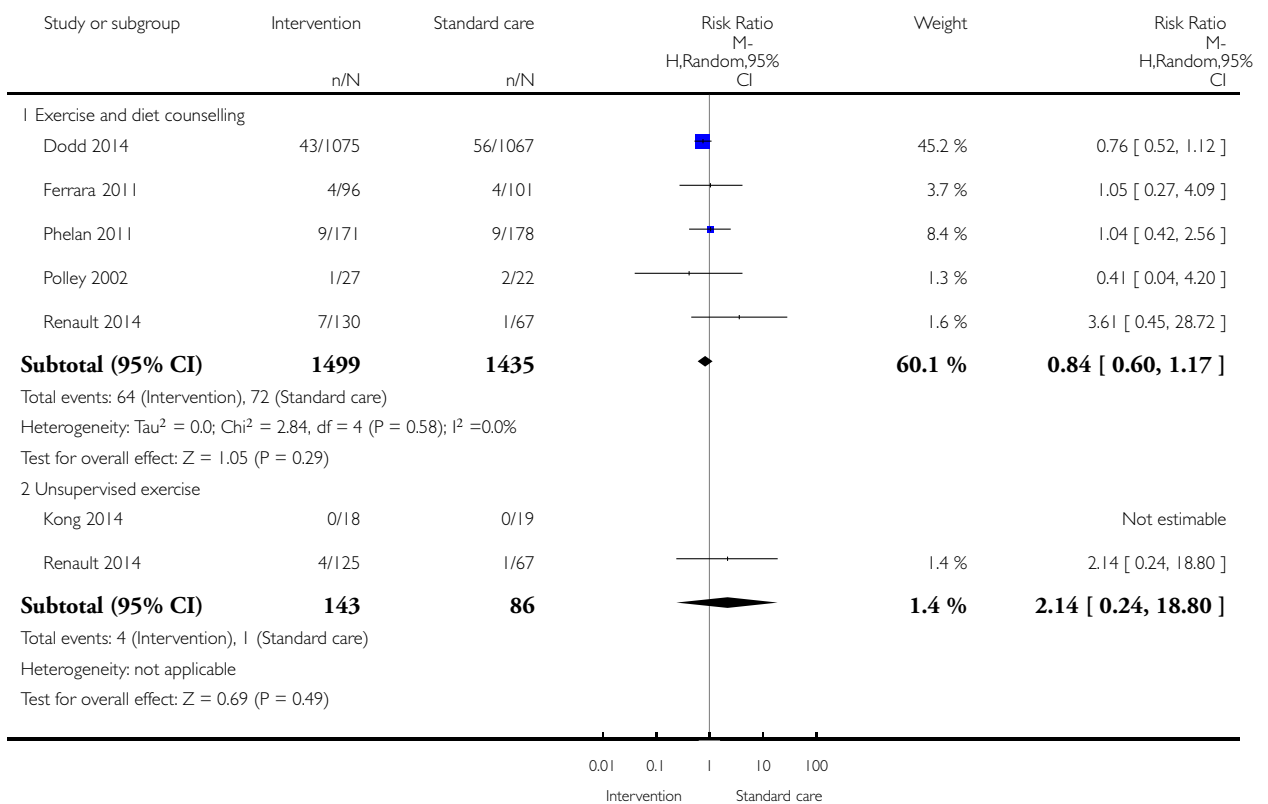
- (1) normal weight women
- (2) overweight women
- (3) combine overweight and obese women
- (4) intervention from 13 weeks
- (5) intervention from 20 weeks
- (6) missing data >45%

Analysis 1.17. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 17 Infant birthweight < 2500 g.

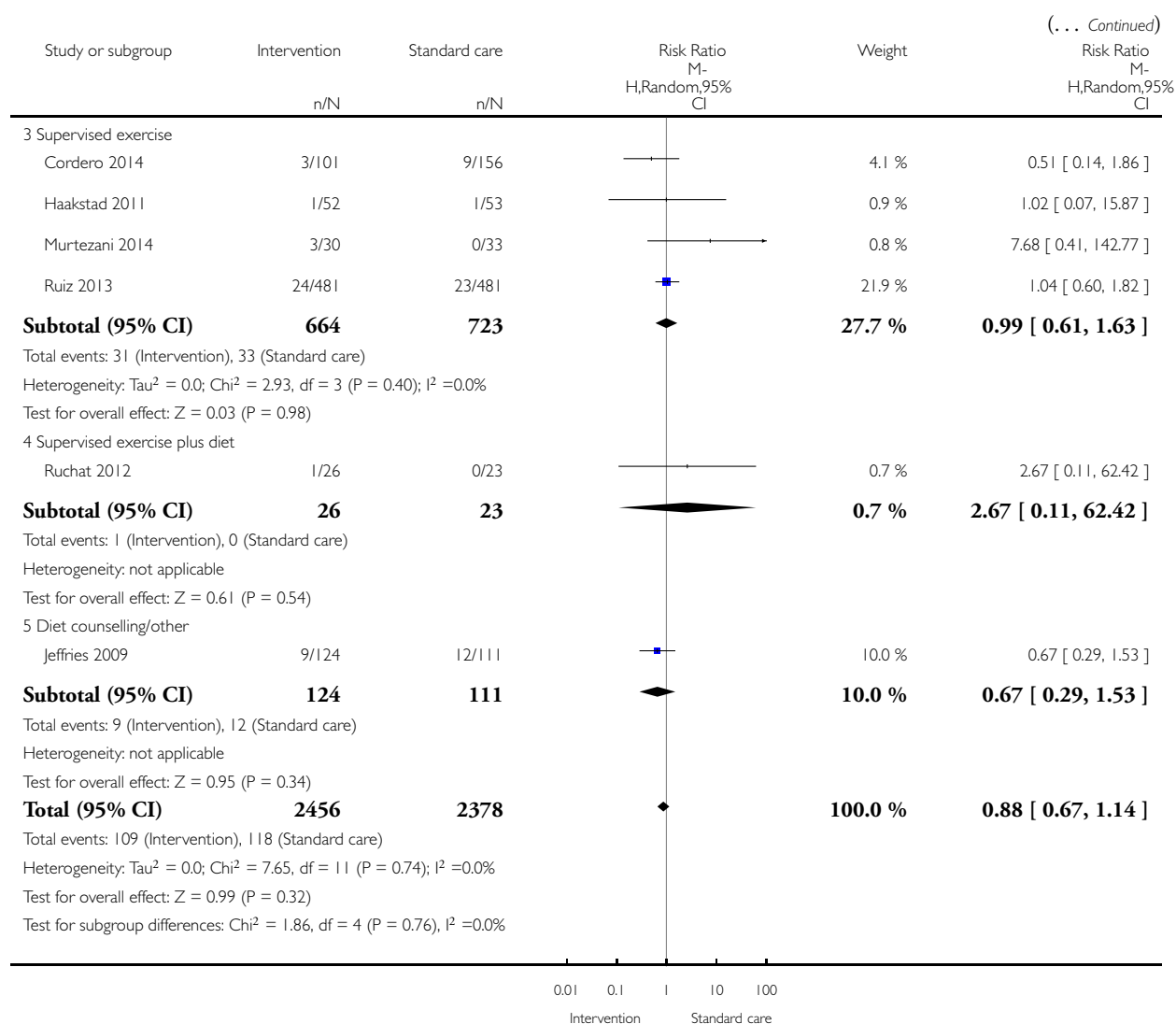
Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 1 All diet and/or exercise interventions vs standard/other care

Outcome: 17 Infant birthweight < 2500 g



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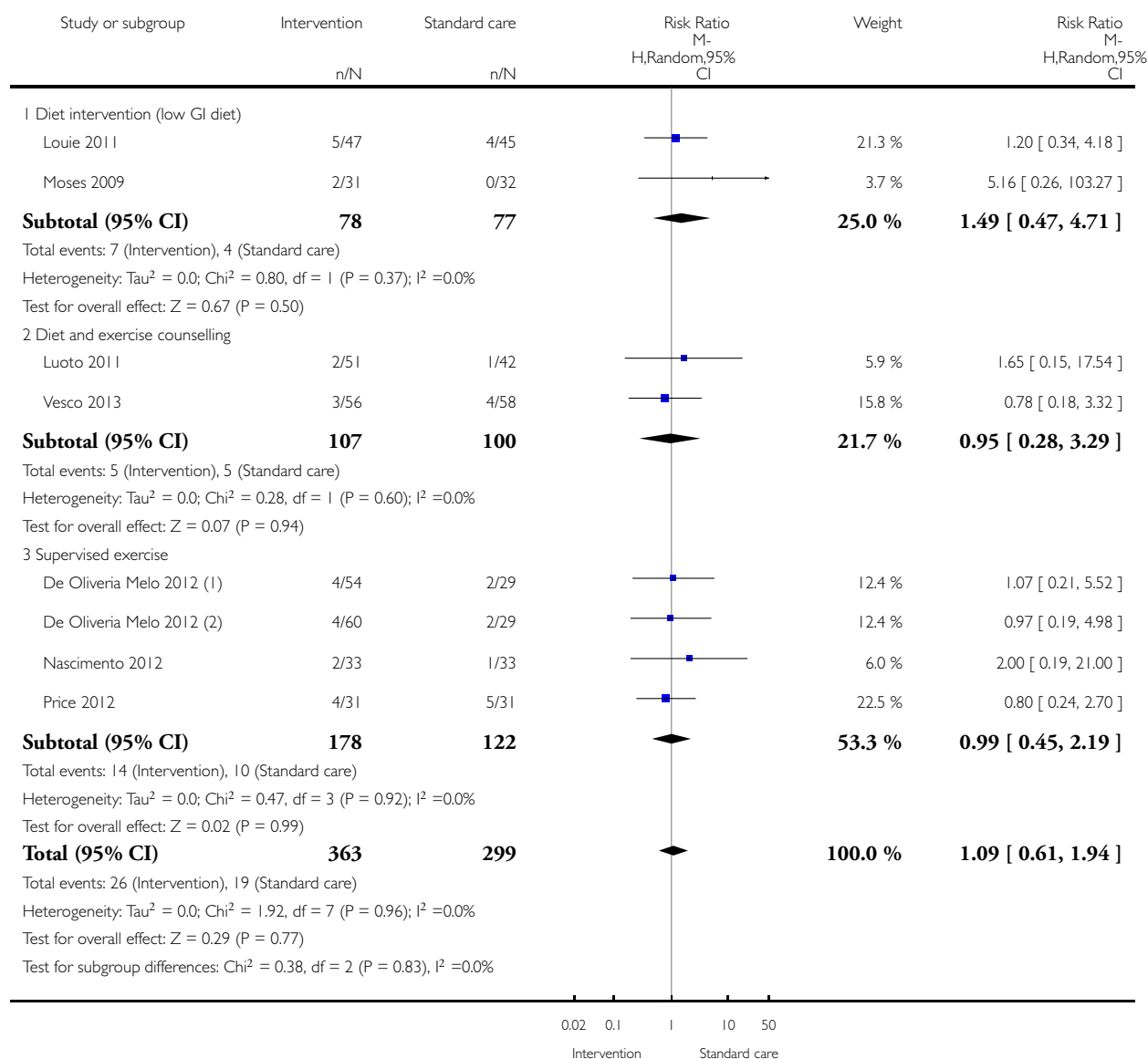


Analysis 1.18. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 18 Infant birthweight < 10th centile.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 1 All diet and/or exercise interventions vs standard/other care

Outcome: 18 Infant birthweight < 10th centile



(1) intervention from 13 weeks

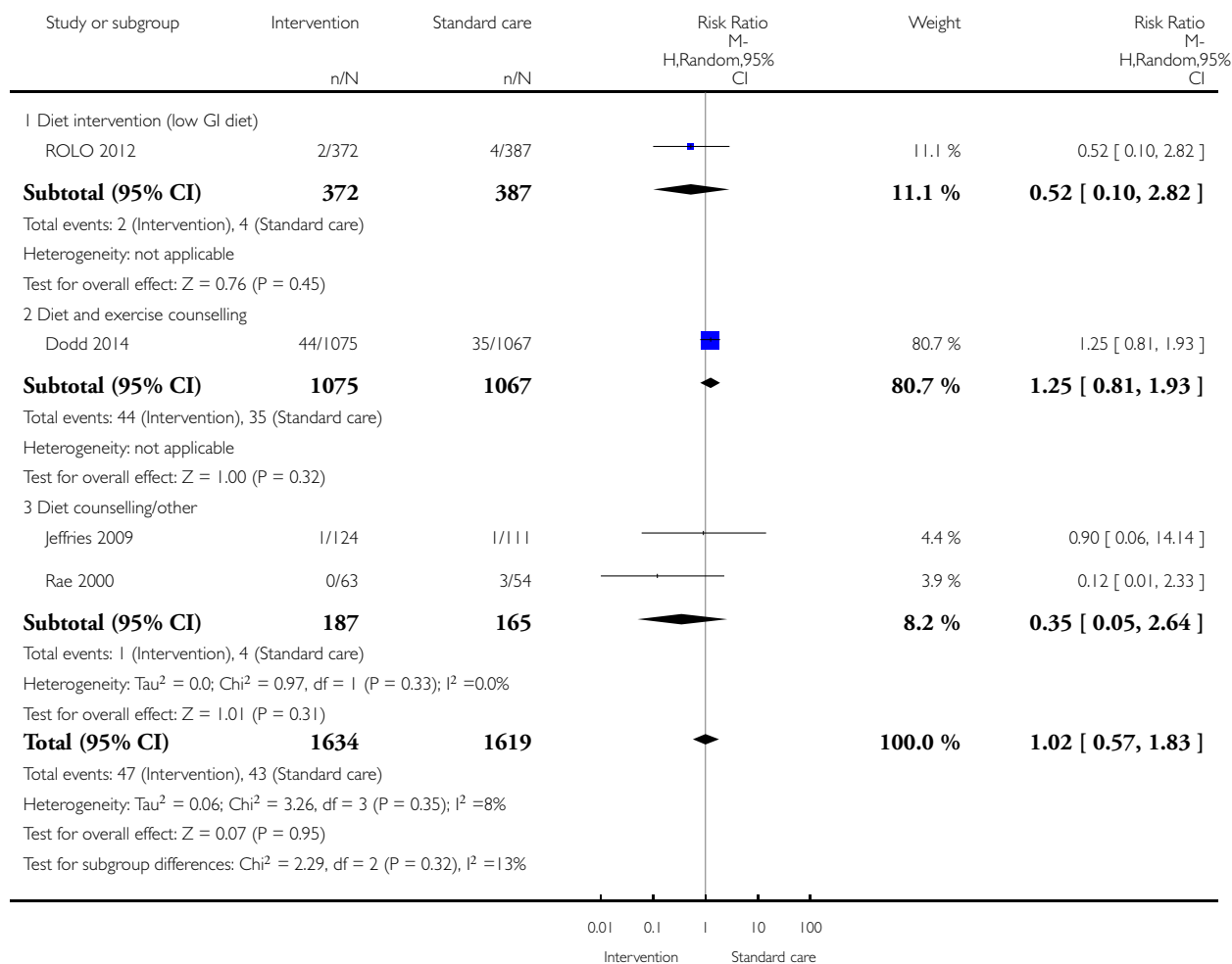
(2) intervention from 20 weeks

Analysis 1.19. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 19 Shoulder dystocia.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 1 All diet and/or exercise interventions vs standard/other care

Outcome: 19 Shoulder dystocia

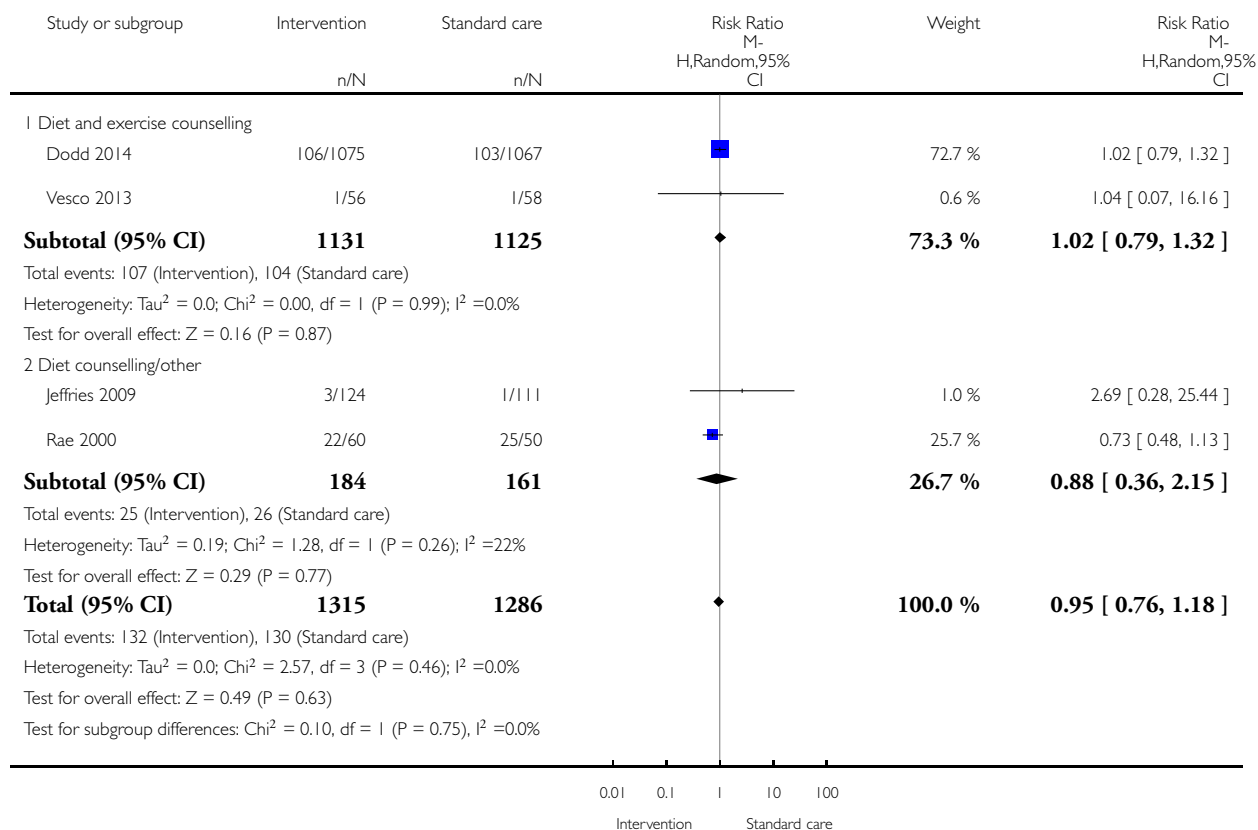


Analysis 1.20. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 20 Neonatal hypoglycaemia.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 1 All diet and/or exercise interventions vs standard/other care

Outcome: 20 Neonatal hypoglycaemia

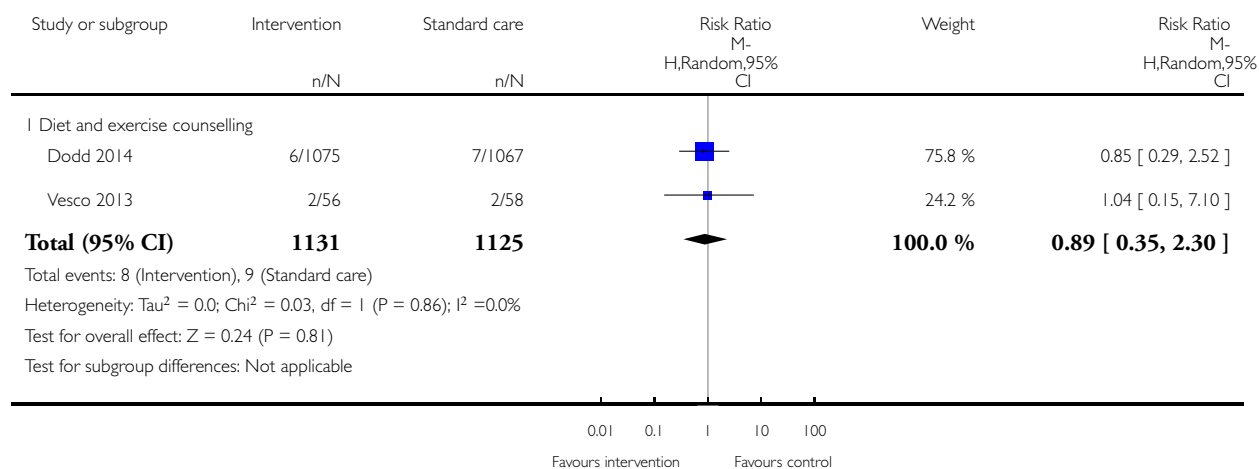


Analysis 1.21. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 21 Birth trauma.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 1 All diet and/or exercise interventions vs standard/other care

Outcome: 21 Birth trauma

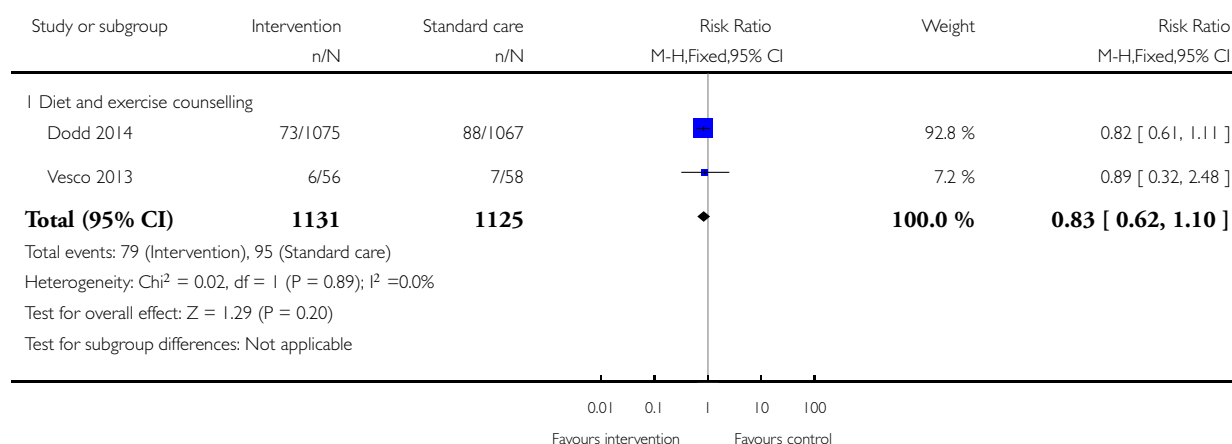


Analysis 1.22. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 22 Neonatal hyperbilirubinaemia.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 1 All diet and/or exercise interventions vs standard/other care

Outcome: 22 Neonatal hyperbilirubinaemia

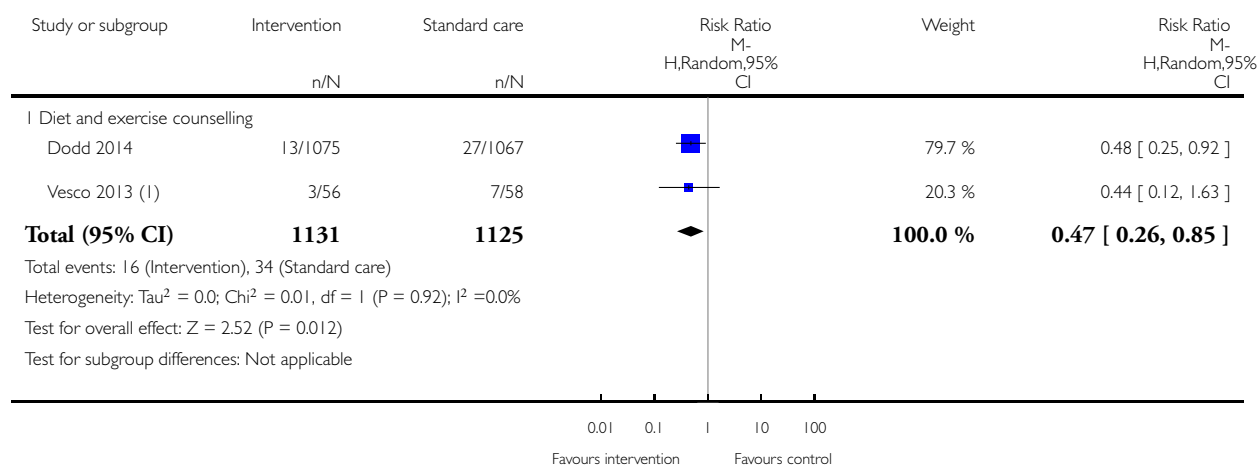


Analysis 1.23. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 23 Neonatal respiratory distress syndrome.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 1 All diet and/or exercise interventions vs standard/other care

Outcome: 23 Neonatal respiratory distress syndrome



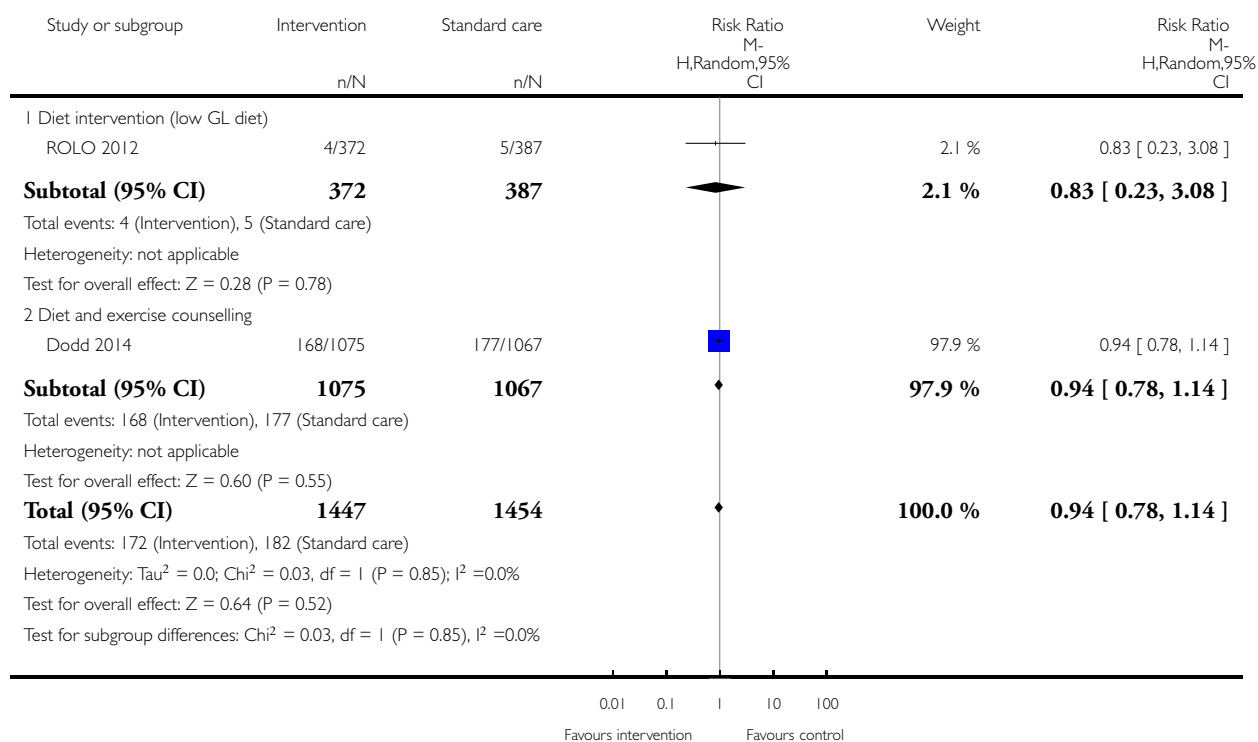
(1) 'respiratory morbidity'

Analysis 1.24. Comparison 1 All diet and/or exercise interventions vs standard/other care, Outcome 24 Postpartum hemorrhage.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 1 All diet and/or exercise interventions vs standard/other care

Outcome: 24 Postpartum hemorrhage

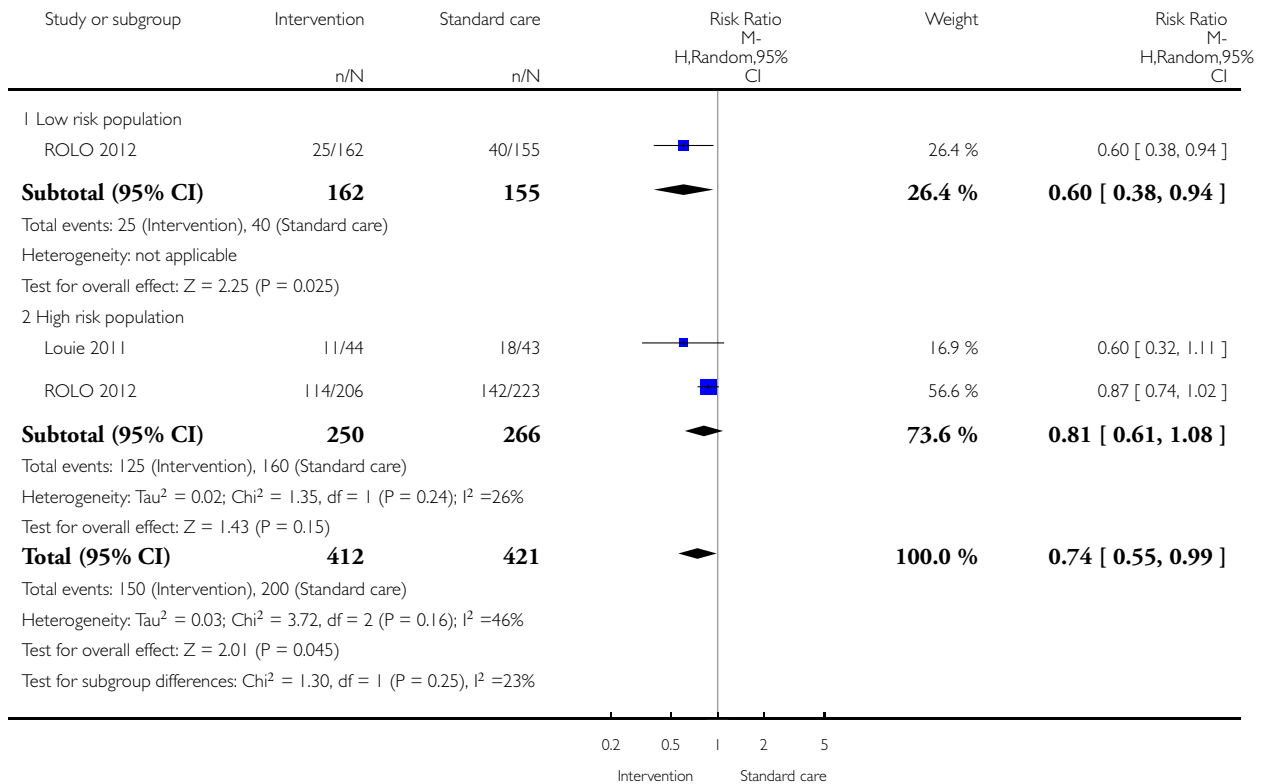


Analysis 2.1. Comparison 2 Diet intervention (low GI diet) vs standard/other care, Outcome 1 Excessive weight gain.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 2 Diet intervention (low GI diet) vs standard/other care

Outcome: 1 Excessive weight gain

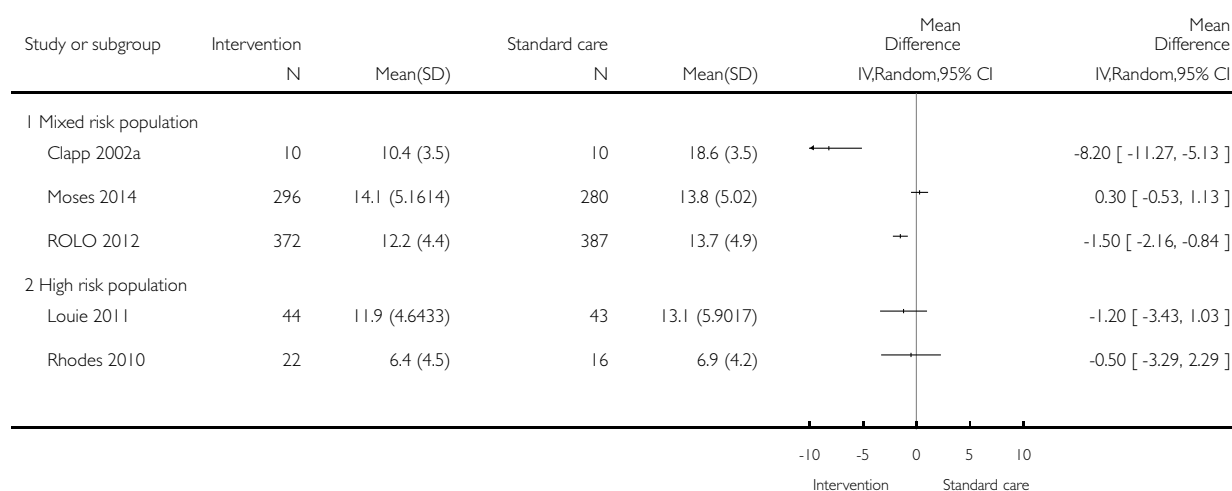


Analysis 2.2. Comparison 2 Diet intervention (low GI diet) vs standard/other care, Outcome 2 Weight gain (kg).

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 2 Diet intervention (low GI diet) vs standard/other care

Outcome: 2 Weight gain (kg)

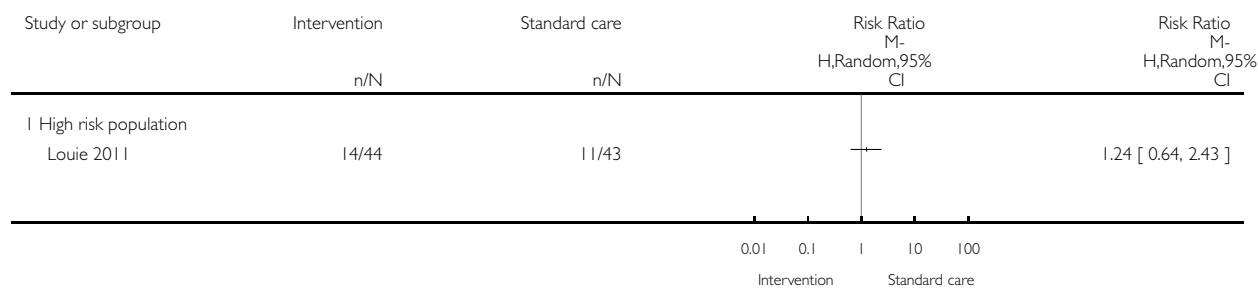


Analysis 2.3. Comparison 2 Diet intervention (low GI diet) vs standard/other care, Outcome 3 Low weight gain.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 2 Diet intervention (low GI diet) vs standard/other care

Outcome: 3 Low weight gain

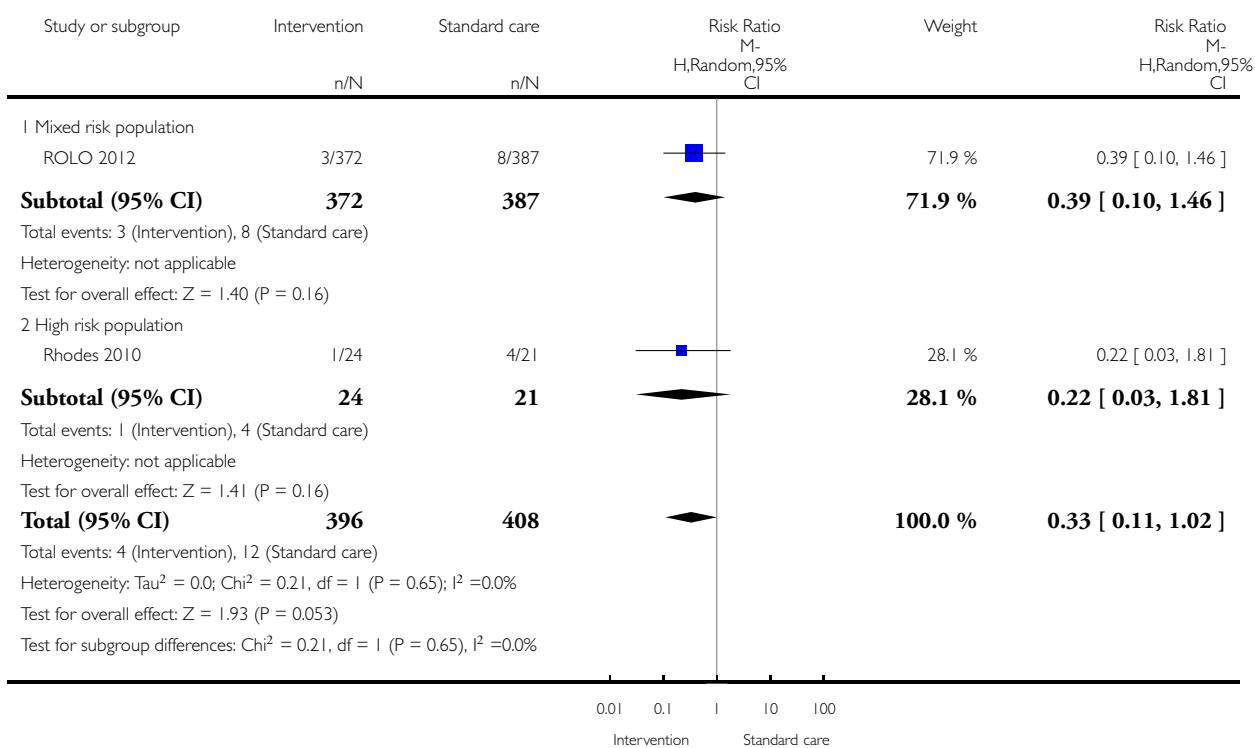


Analysis 2.4. Comparison 2 Diet intervention (low GI diet) vs standard/other care, Outcome 4 Preterm birth.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 2 Diet intervention (low GI diet) vs standard/other care

Outcome: 4 Preterm birth

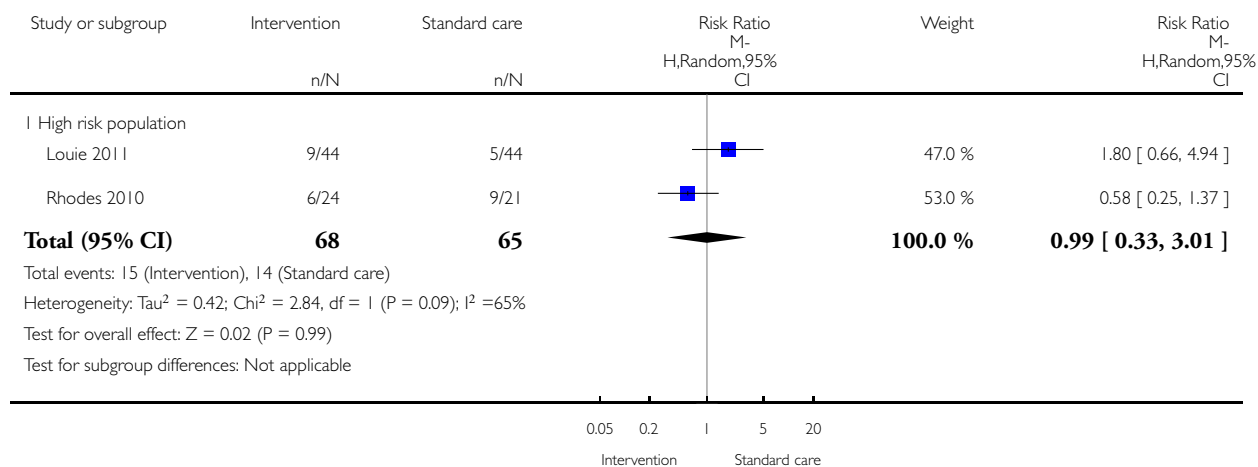


Analysis 2.5. Comparison 2 Diet intervention (low GI diet) vs standard/other care, Outcome 5 Caesarean delivery.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 2 Diet intervention (low GI diet) vs standard/other care

Outcome: 5 Caesarean delivery

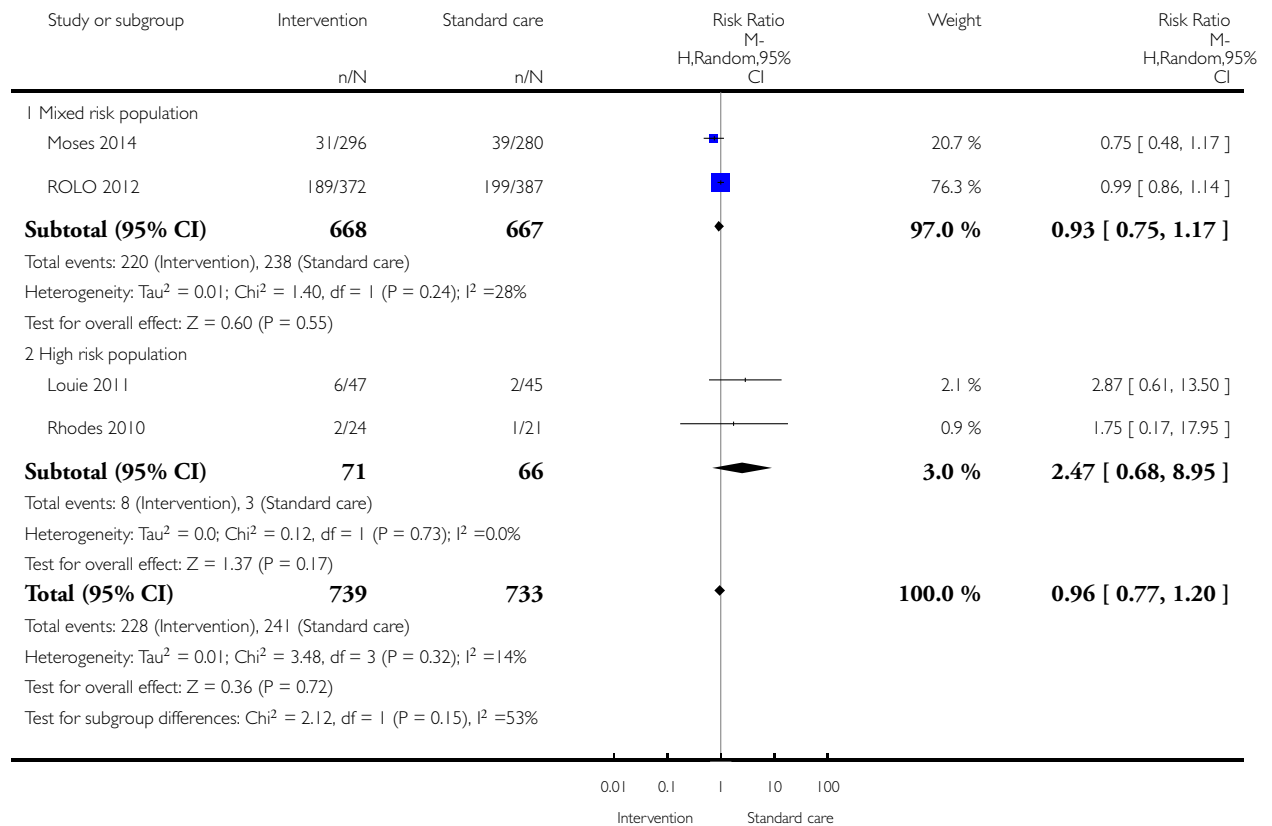


Analysis 2.6. Comparison 2 Diet intervention (low GI diet) vs standard/other care, Outcome 6 Macrosomia (Infant birthweight > 4000 g).

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 2 Diet intervention (low GI diet) vs standard/other care

Outcome: 6 Macrosomia (Infant birthweight > 4000 g)

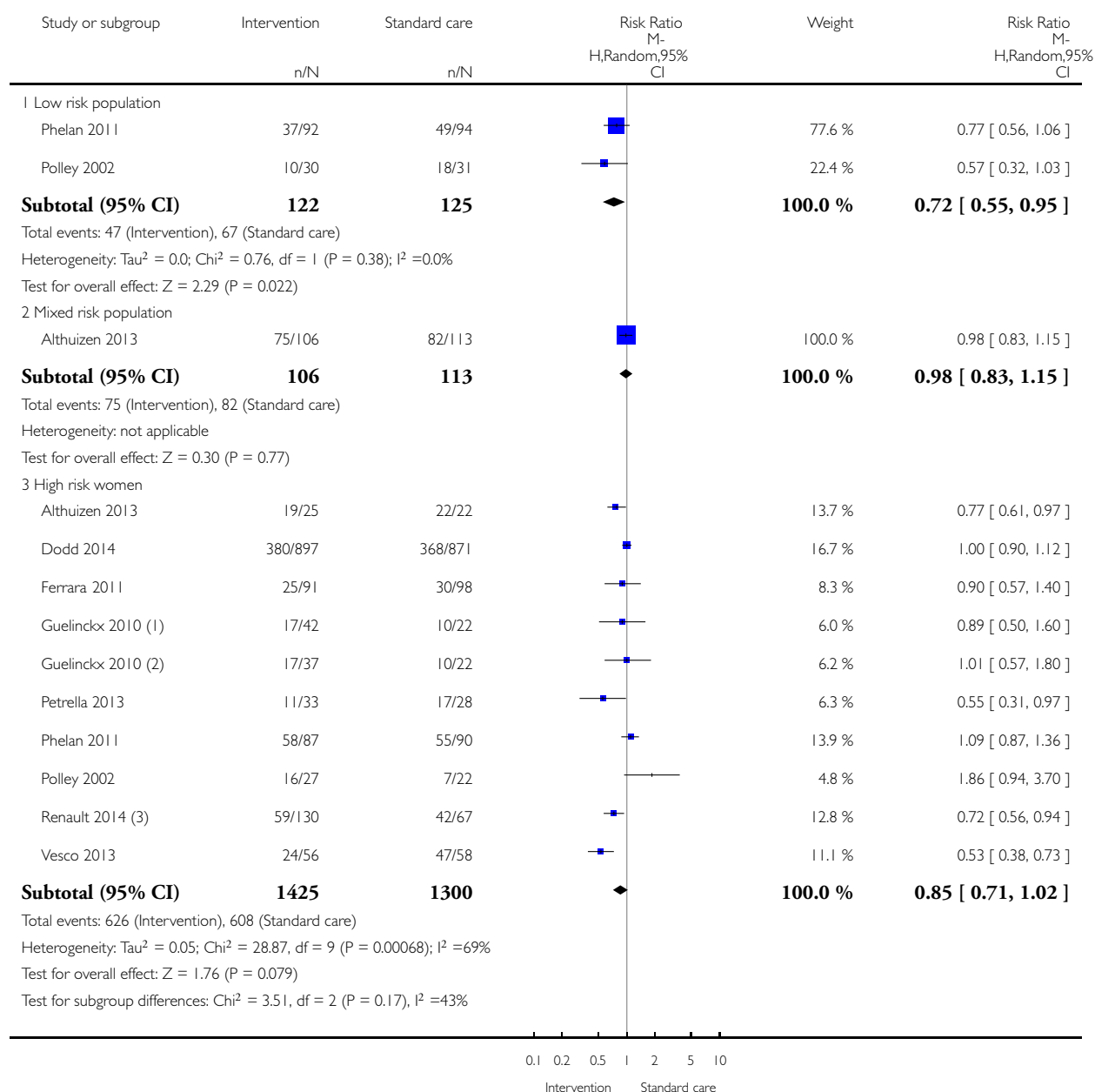


Analysis 3.1. Comparison 3 Diet and exercise counselling vs standard/other care, Outcome 1 Excessive weight gain.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 3 Diet and exercise counselling vs standard/other care

Outcome: 1 Excessive weight gain



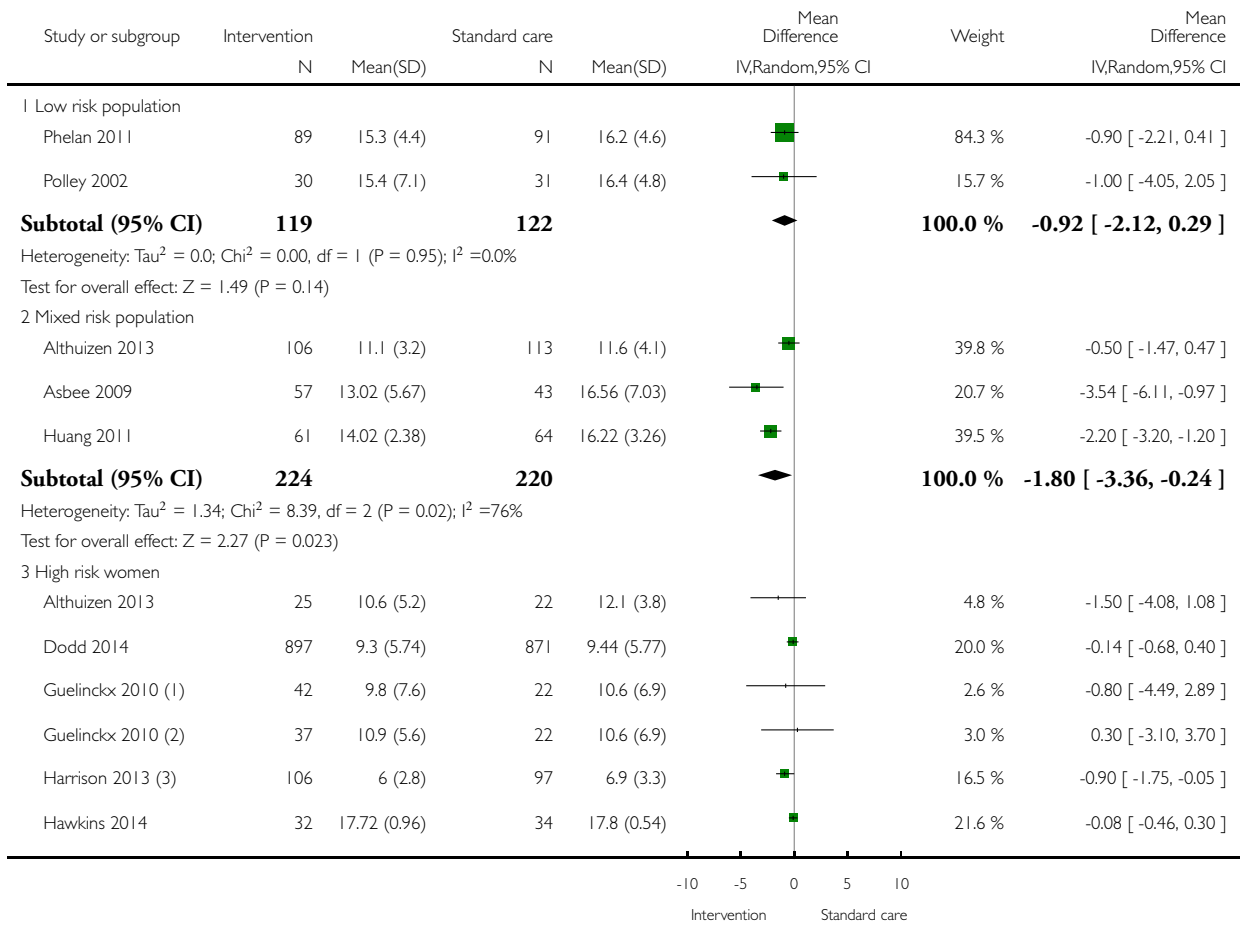
- (1) diet counselling plus brochure
- (2) nutritional advice from a brochure
- (3) 3-arms: control group halved

Analysis 3.2. Comparison 3 Diet and exercise counselling vs standard/other care, Outcome 2 Weight gain (kg).

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

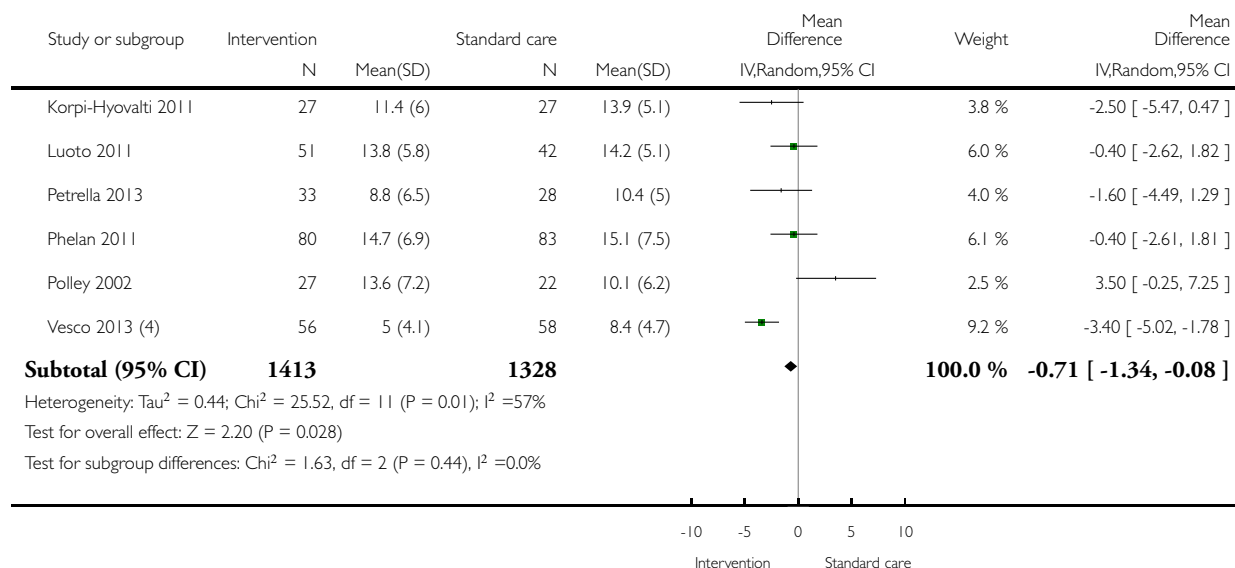
Comparison: 3 Diet and exercise counselling vs standard/other care

Outcome: 2 Weight gain (kg)



(Continued ...)

(... Continued)



(1) diet counselling plus brochure

(2) brochure only

(3) measured at 26-28 weeks

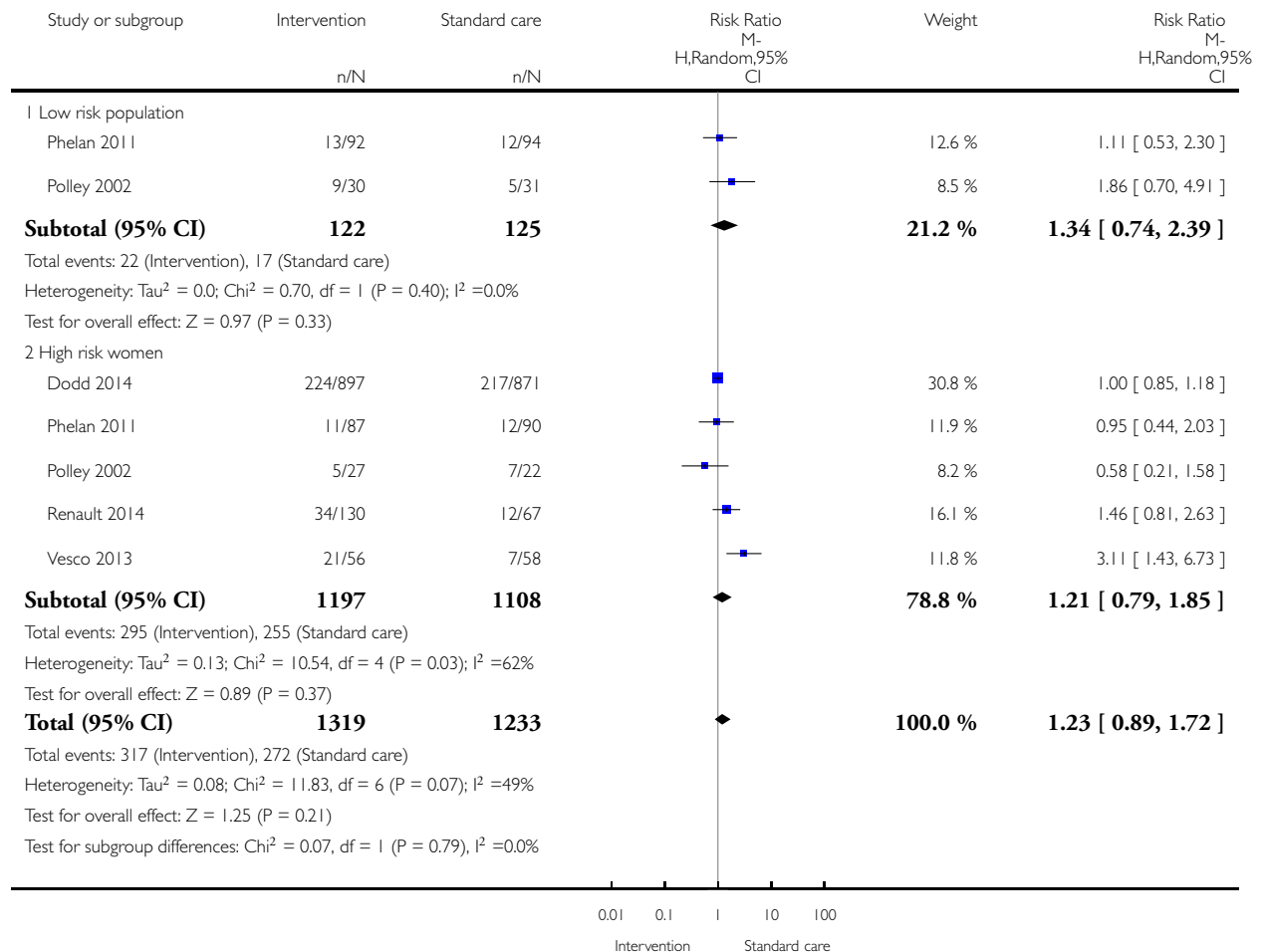
(4) measured at 34 weeks

Analysis 3.3. Comparison 3 Diet and exercise counselling vs standard/other care, Outcome 3 Low weight gain.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 3 Diet and exercise counselling vs standard/other care

Outcome: 3 Low weight gain

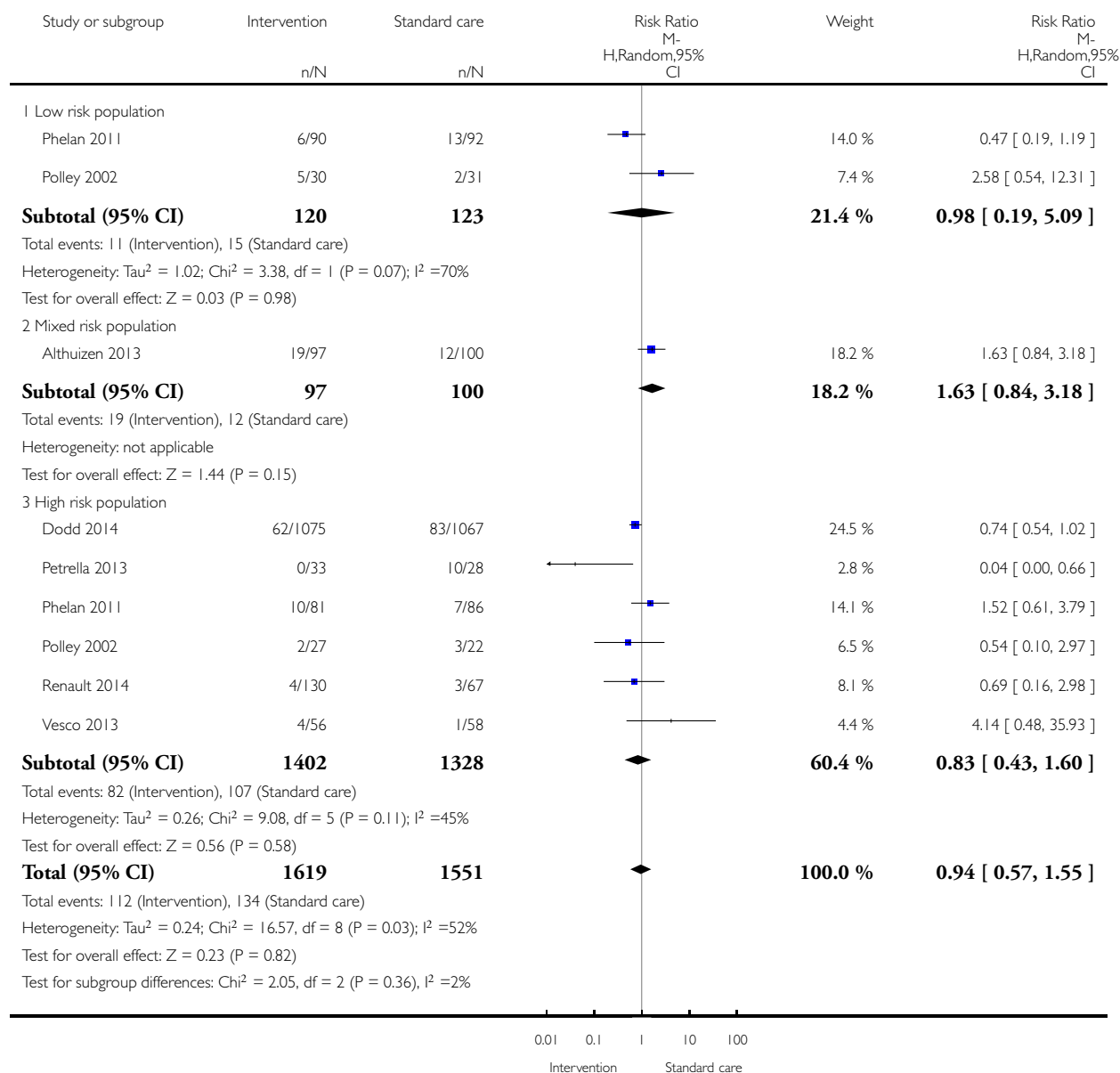


Analysis 3.4. Comparison 3 Diet and exercise counselling vs standard/other care, Outcome 4 Preterm birth.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 3 Diet and exercise counselling vs standard/other care

Outcome: 4 Preterm birth

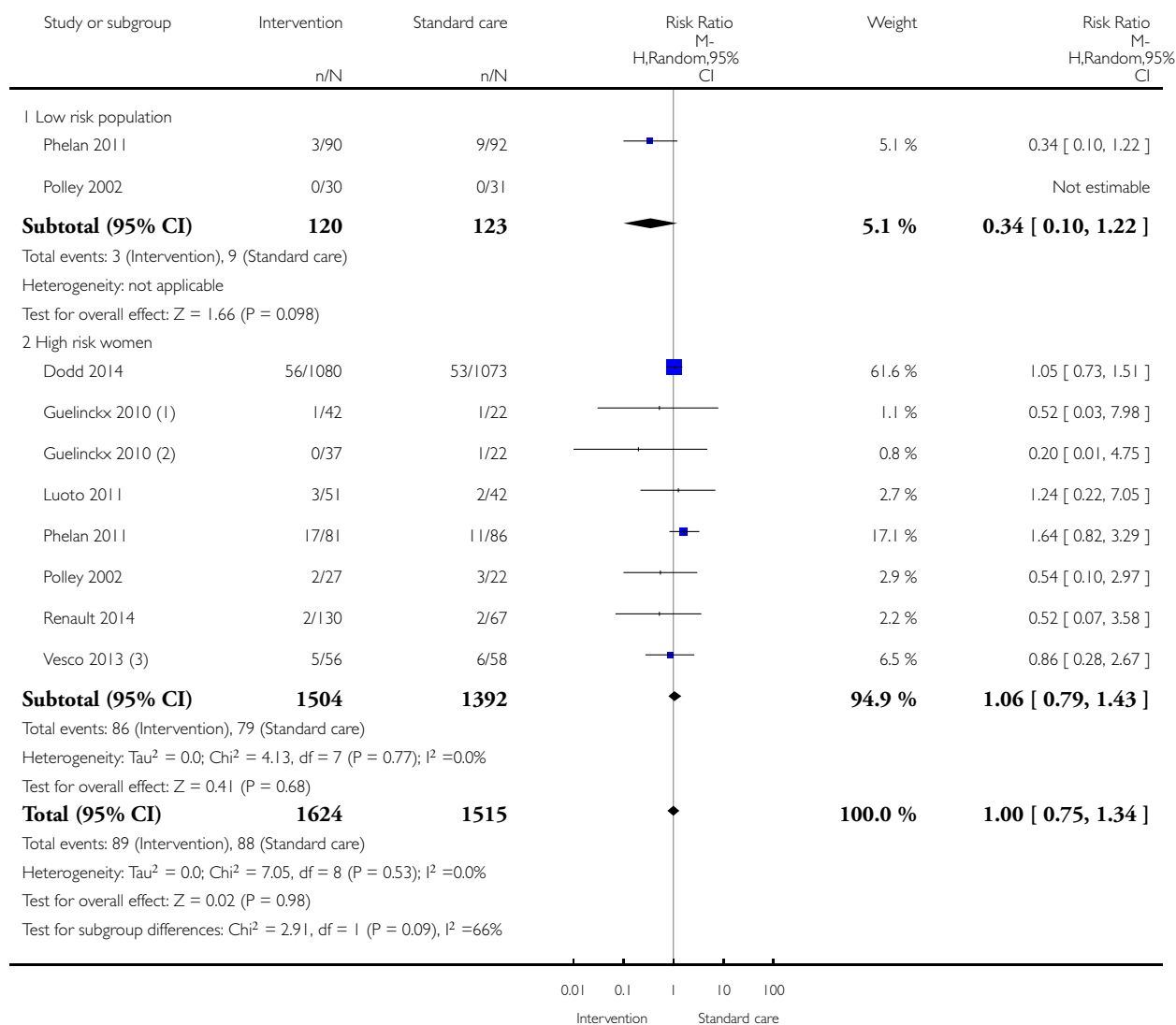


Analysis 3.5. Comparison 3 Diet and exercise counselling vs standard/other care, Outcome 5 Pre-eclampsia.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 3 Diet and exercise counselling vs standard/other care

Outcome: 5 Pre-eclampsia



(1) Counselling and brochure

(2) Brochure only

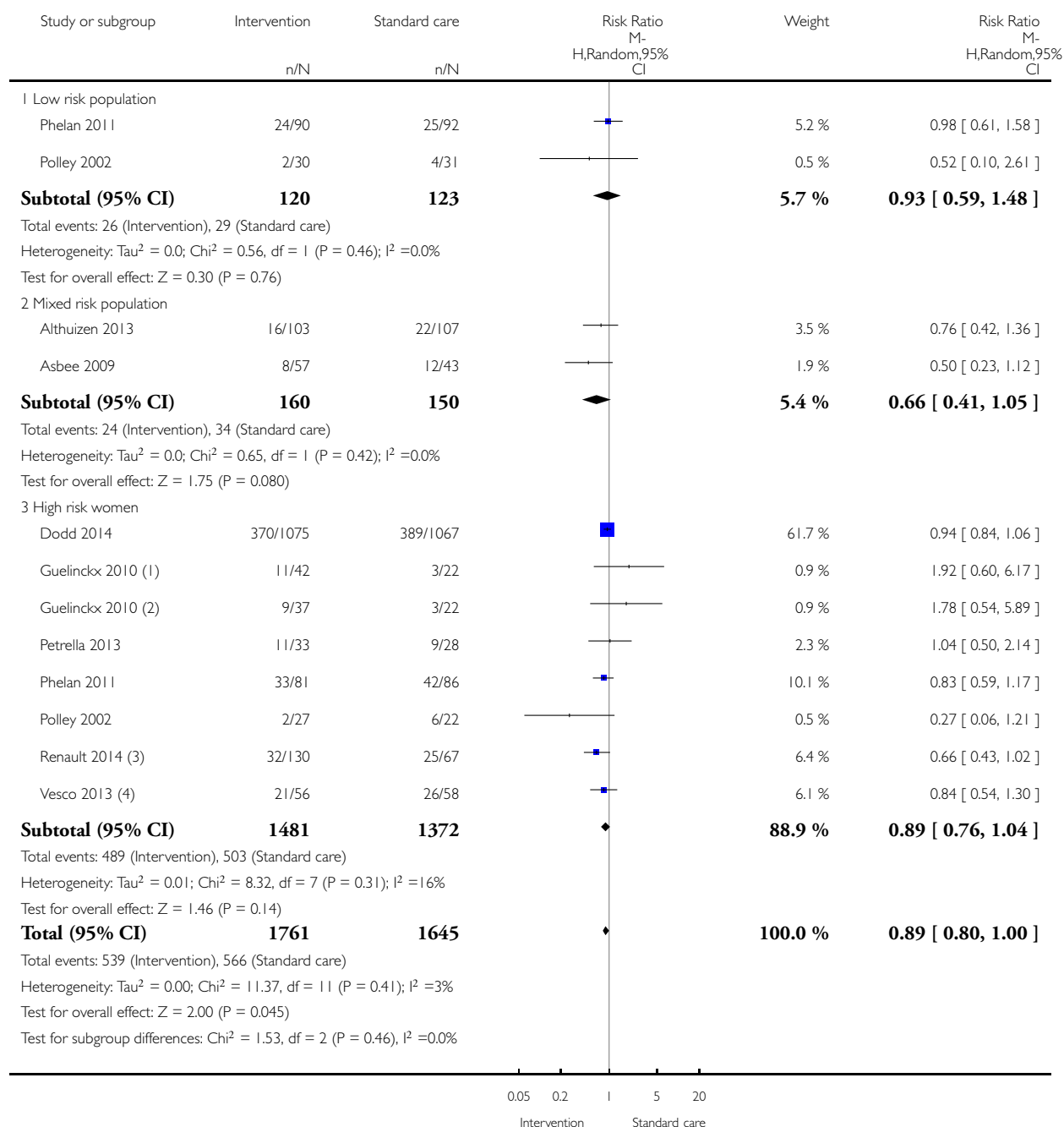
(3) PE/PIH

Analysis 3.6. Comparison 3 Diet and exercise counselling vs standard/other care, Outcome 6 Caesarean delivery.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 3 Diet and exercise counselling vs standard/other care

Outcome: 6 Caesarean delivery



(1) Counselling plus brochure

(2) Brochure only

(3) obese women

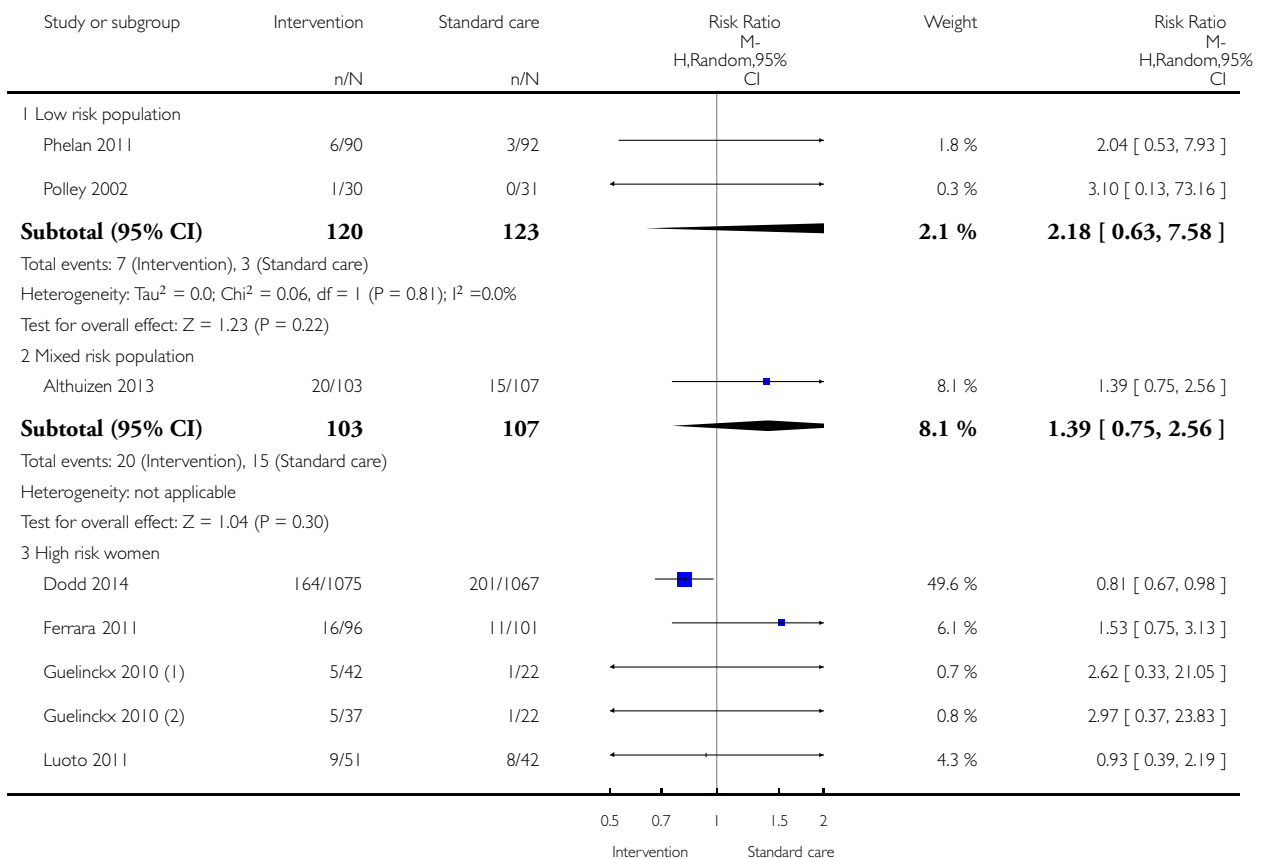
(4) obese women

Analysis 3.7. Comparison 3 Diet and exercise counselling vs standard/other care, Outcome 7 Macrosomia (Infant birthweight > 4000 g).

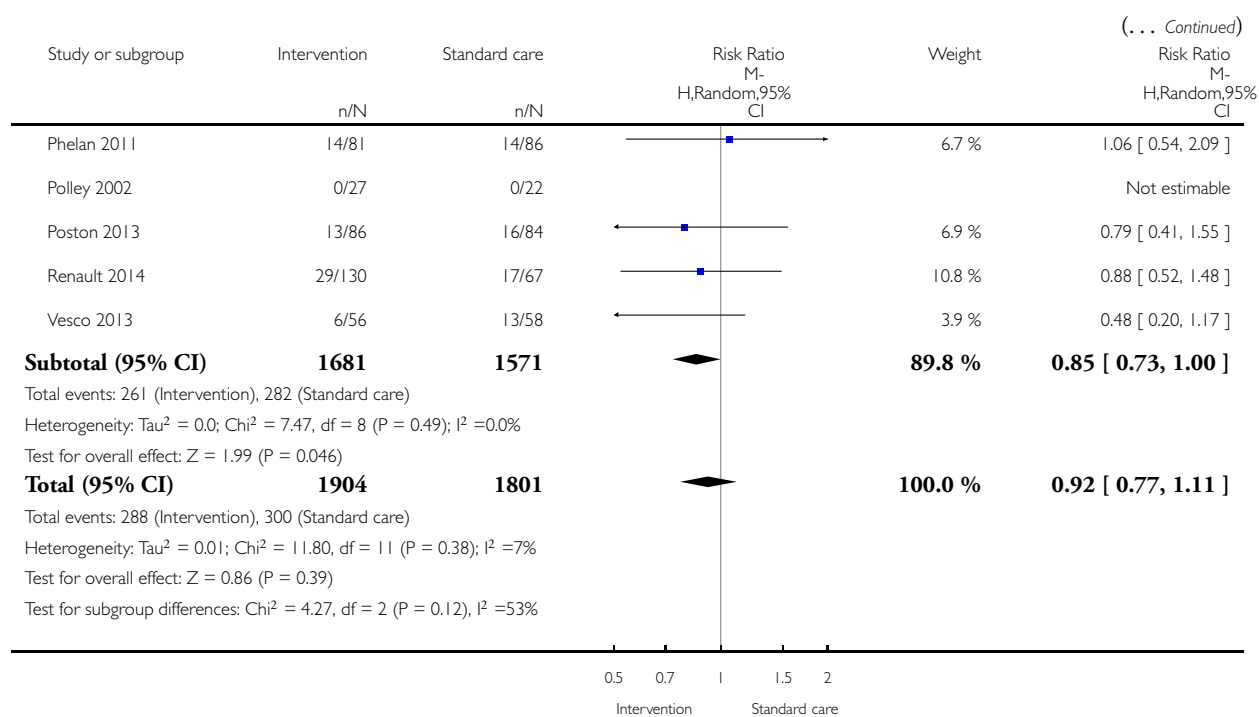
Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 3 Diet and exercise counselling vs standard/other care

Outcome: 7 Macrosomia (Infant birthweight > 4000 g)



(Continued ...)



(1) Counselling plus brochure

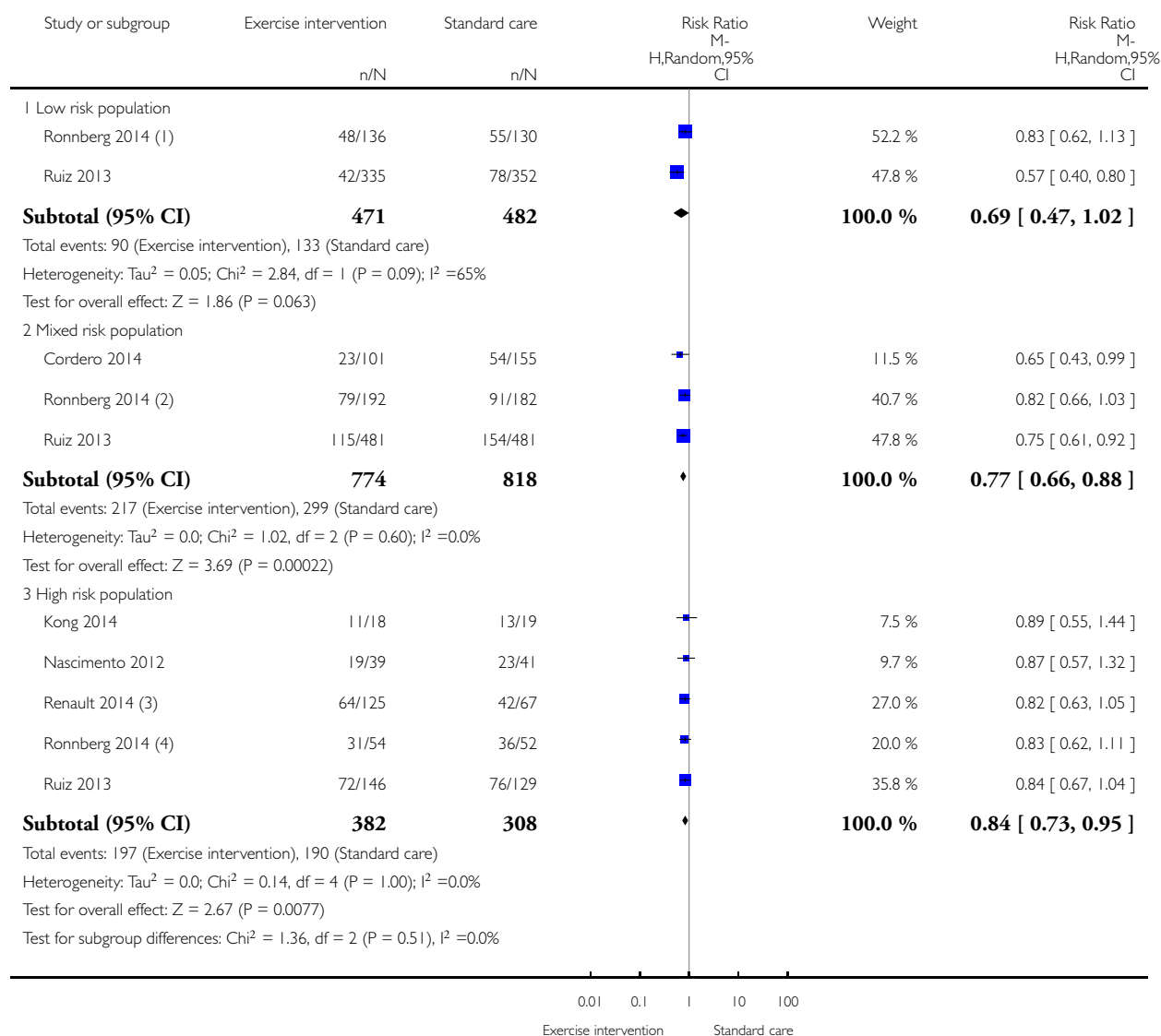
(2) Brochure only

Analysis 4.1. Comparison 4 Exercise vs standard/other care, Outcome 1 Excessive weight gain.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 4 Exercise vs standard/other care

Outcome: 1 Excessive weight gain



(1) BMI 19 to 26 kg/m²

(2) unsupervised exercise

(3) 3-arms: control group halved

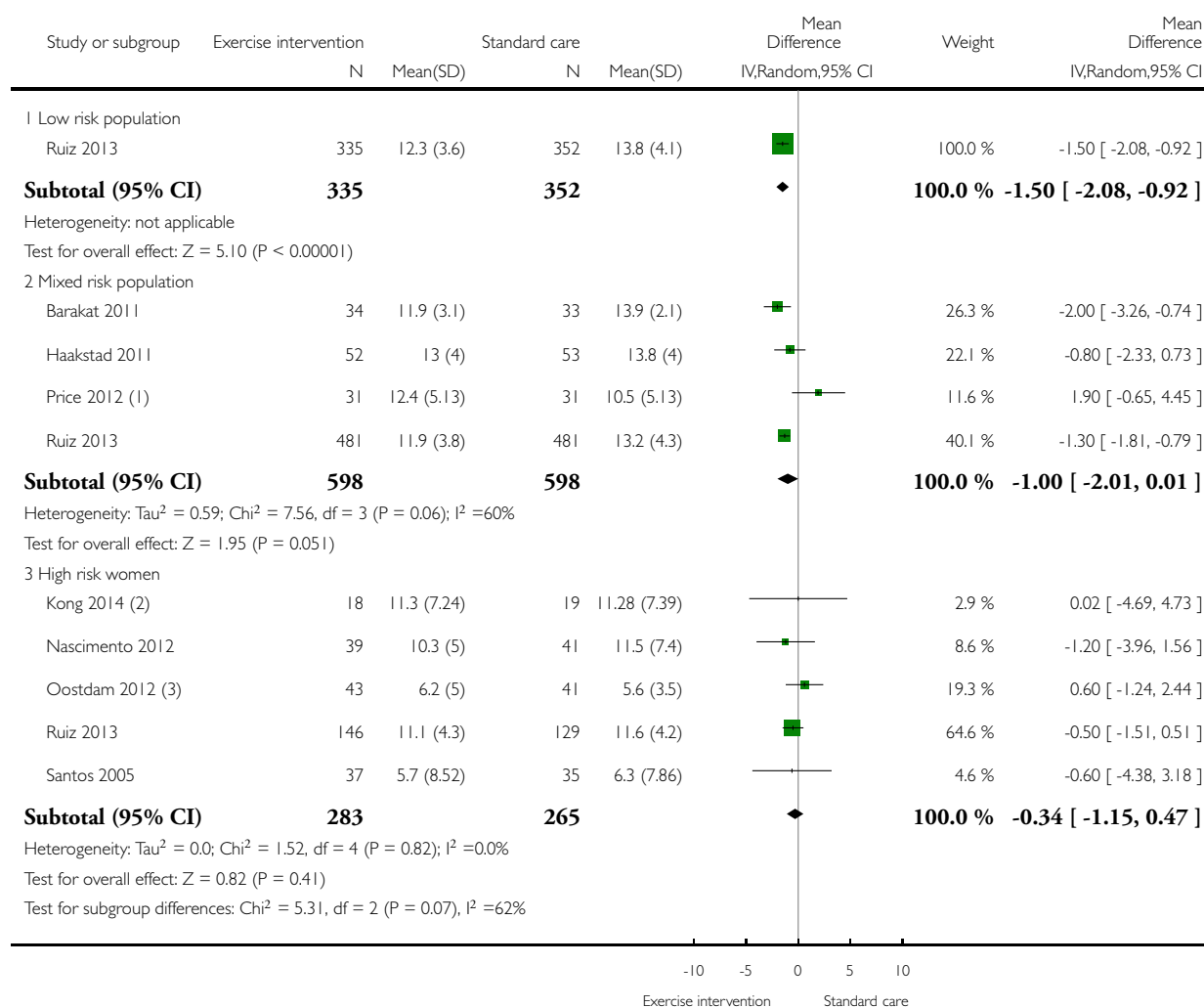
(4) unsupervised exercise

Analysis 4.2. Comparison 4 Exercise vs standard/other care, Outcome 2 Weight gain (kg).

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 4 Exercise vs standard/other care

Outcome: 2 Weight gain (kg)



(1) high risk of bias

(2) combine overweight and obese women

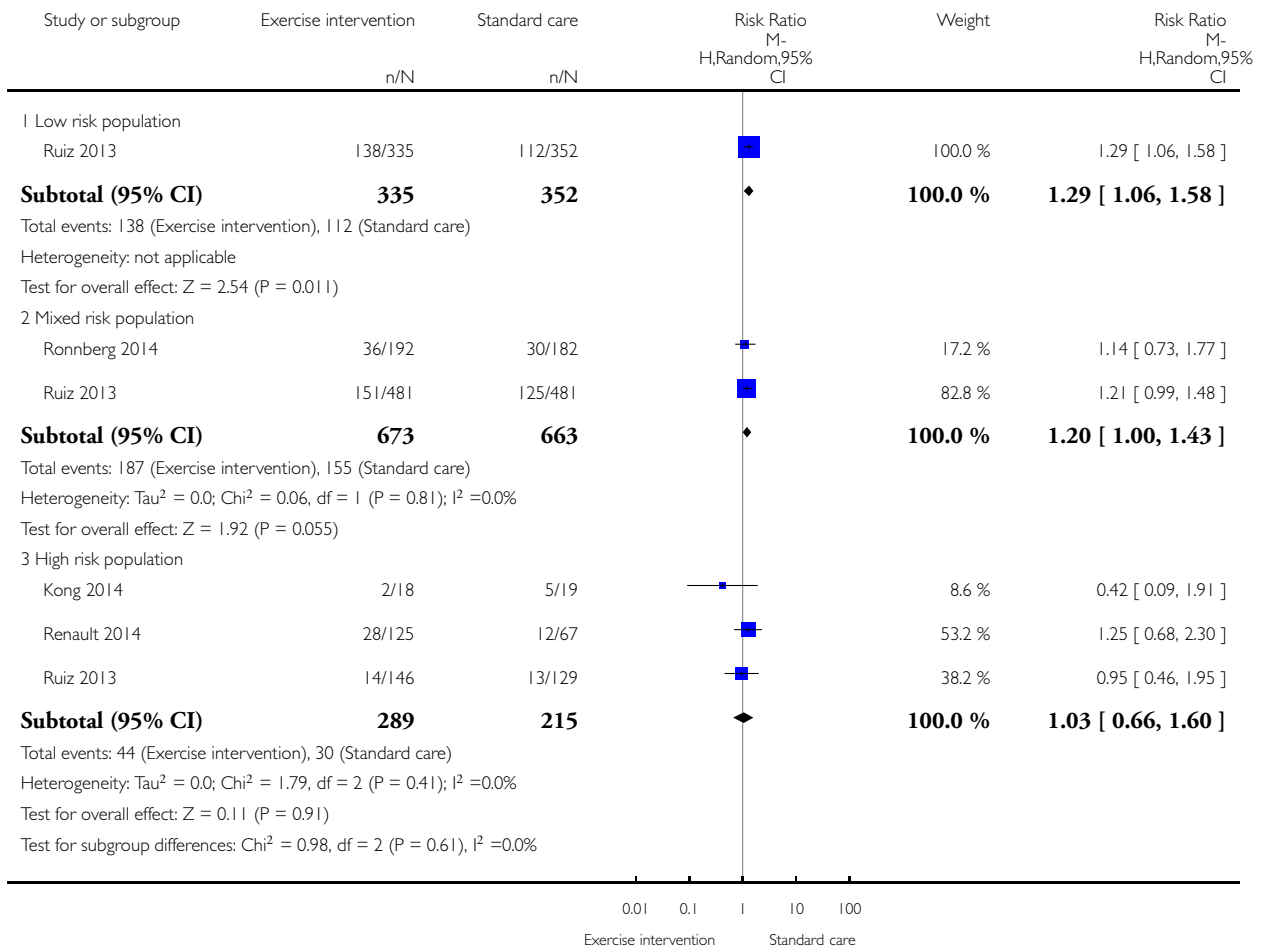
(3) 31% missing data

Analysis 4.3. Comparison 4 Exercise vs standard/other care, Outcome 3 Low weight gain.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 4 Exercise vs standard/other care

Outcome: 3 Low weight gain

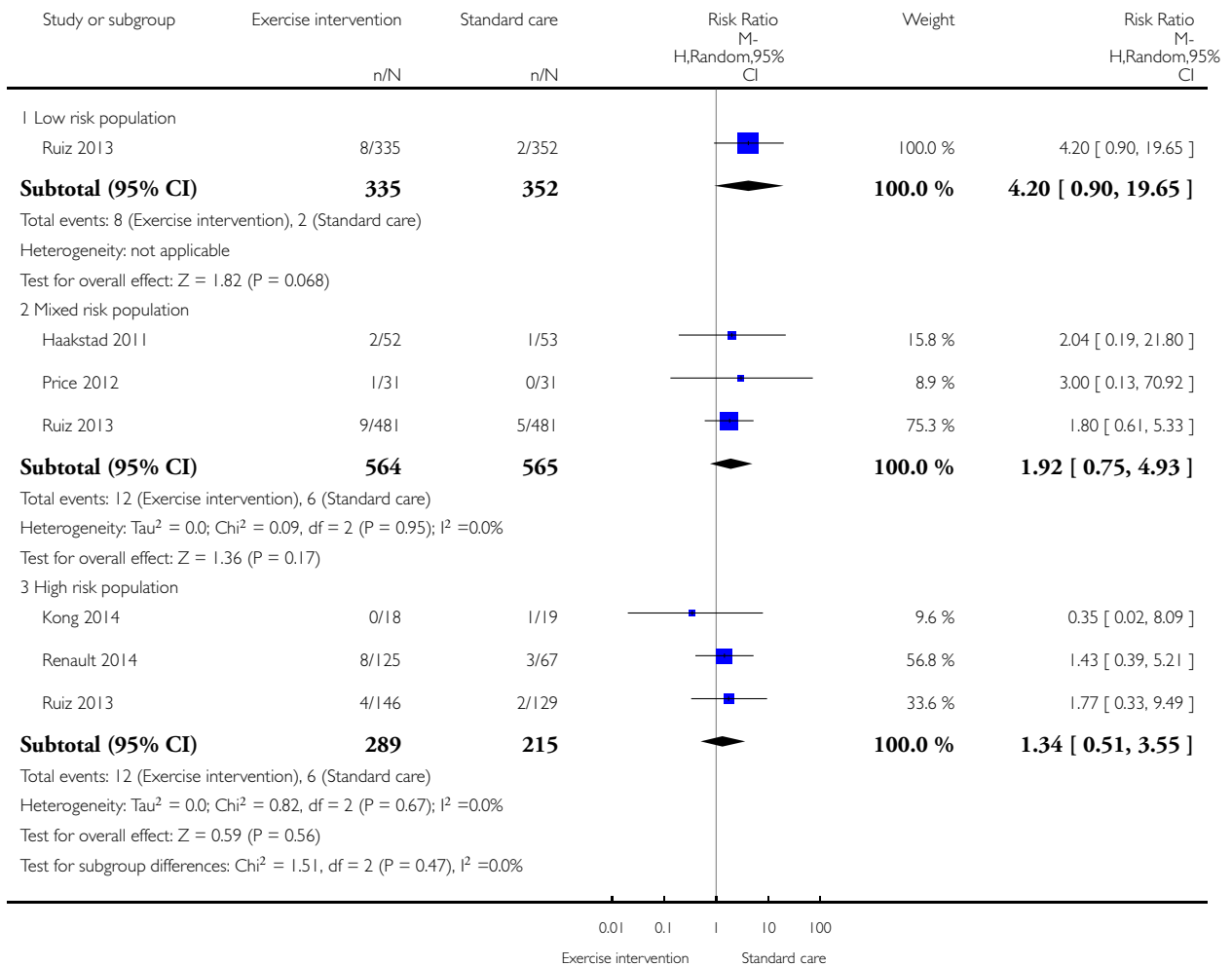


Analysis 4.4. Comparison 4 Exercise vs standard/other care, Outcome 4 Preterm birth.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 4 Exercise vs standard/other care

Outcome: 4 Preterm birth

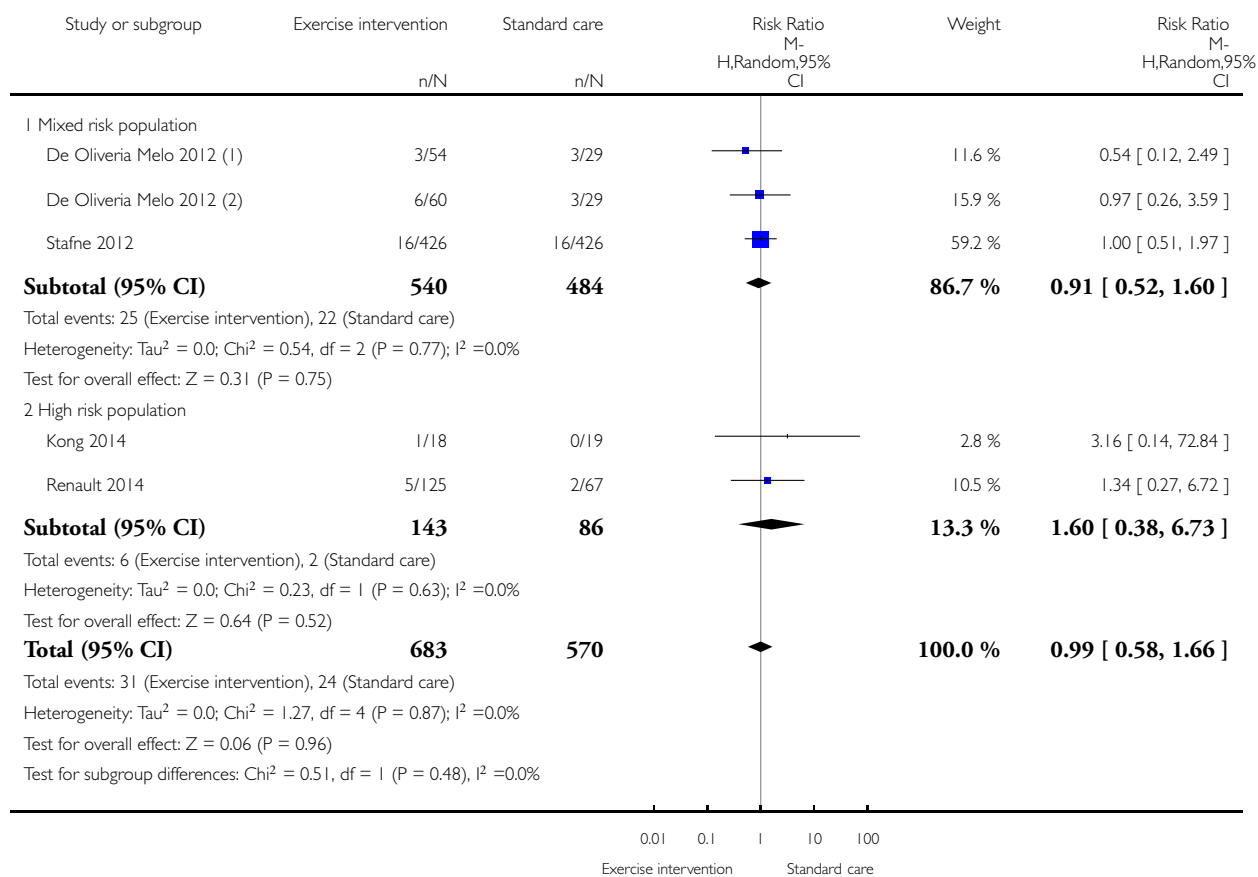


Analysis 4.5. Comparison 4 Exercise vs standard/other care, Outcome 5 Pre-eclampsia.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 4 Exercise vs standard/other care

Outcome: 5 Pre-eclampsia



(1) intervention from 13 weeks

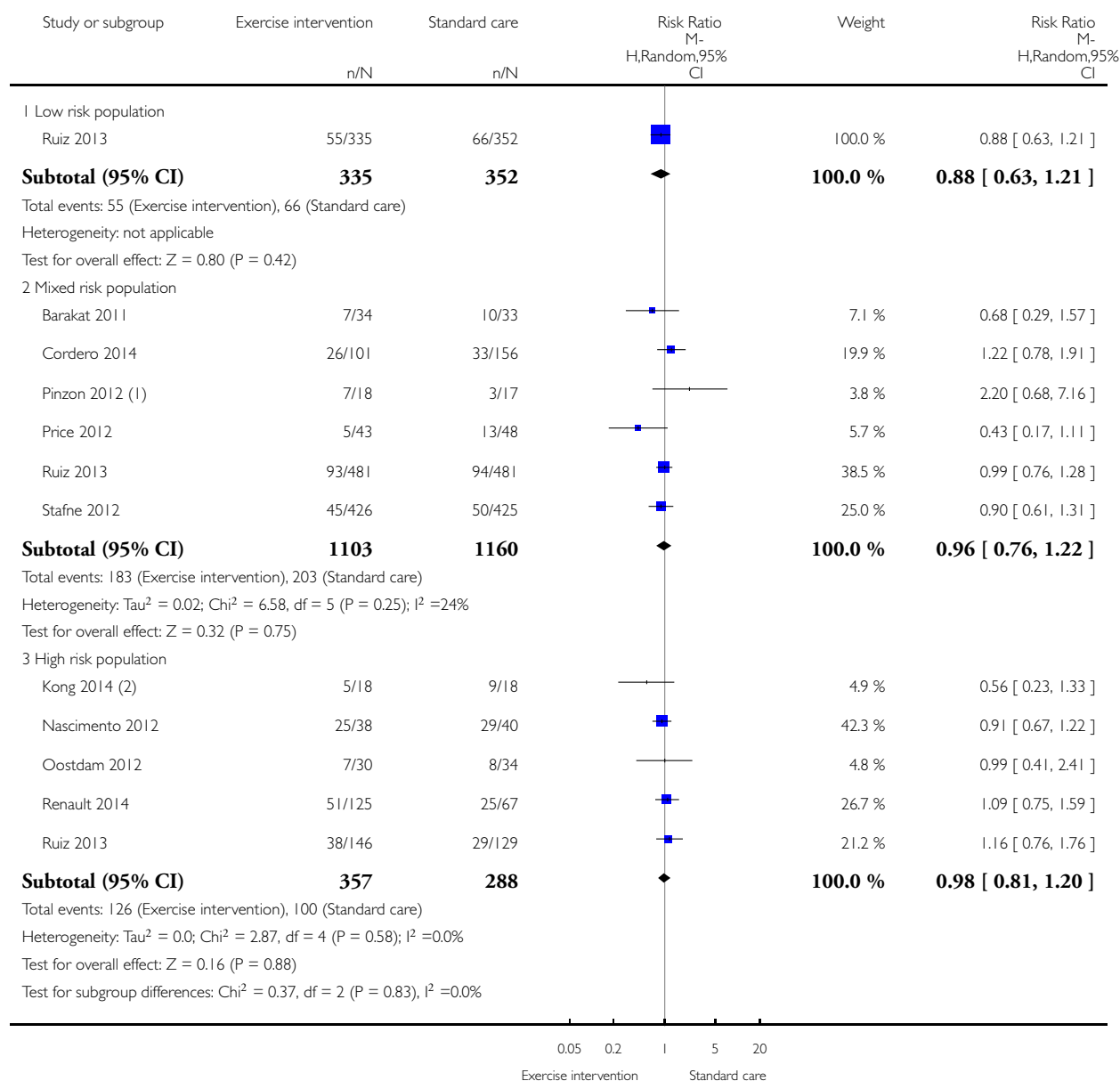
(2) intervention from 20 weeks

Analysis 4.6. Comparison 4 Exercise vs standard/other care, Outcome 6 Caesarean delivery.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 4 Exercise vs standard/other care

Outcome: 6 Caesarean delivery



(1) 45% missing data

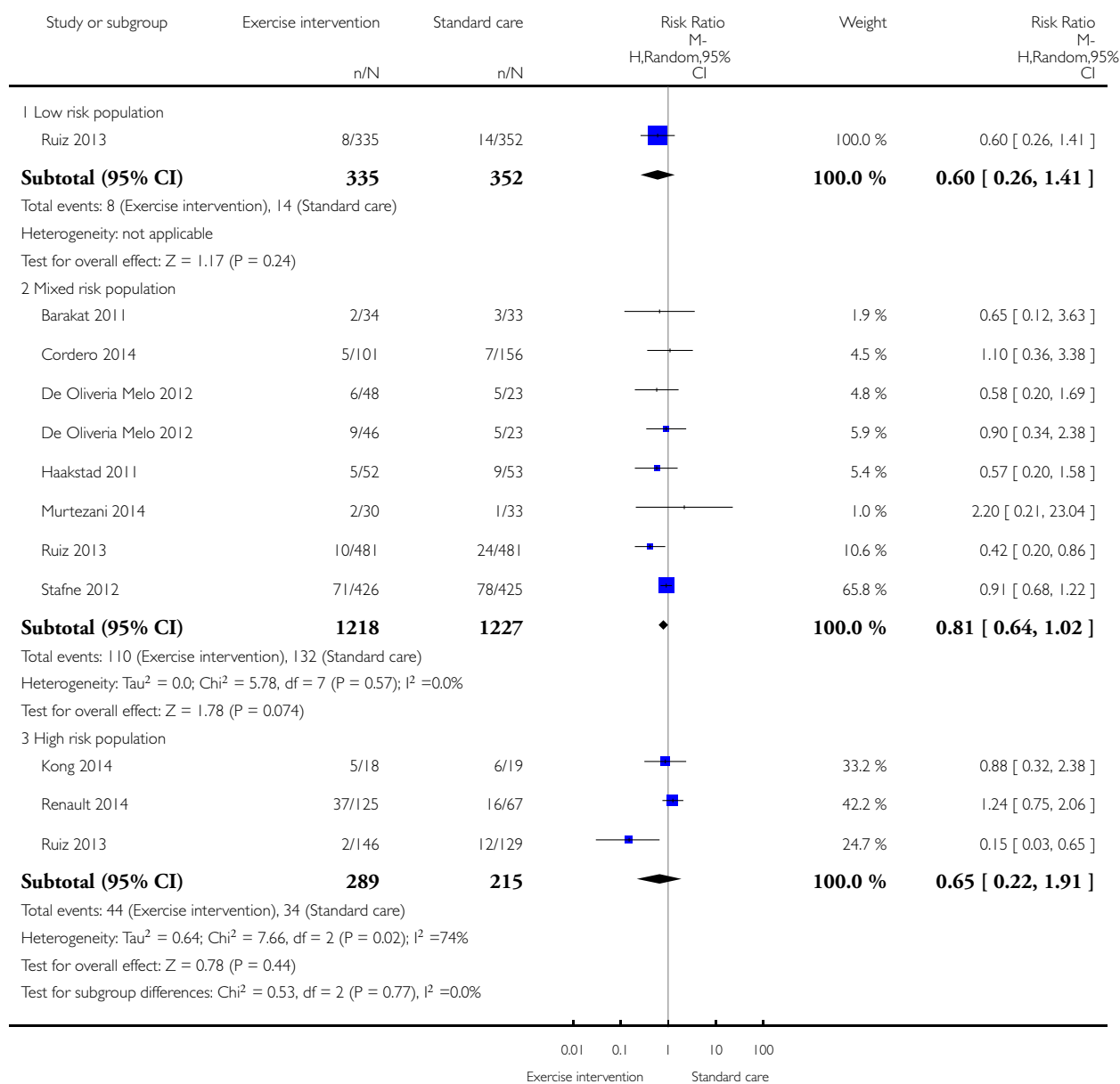
(2) combine overweight and obese women

Analysis 4.7. Comparison 4 Exercise vs standard/other care, Outcome 7 Macrosomia (Infant birthweight > 4000 g).

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 4 Exercise vs standard/other care

Outcome: 7 Macrosomia (Infant birthweight > 4000 g)

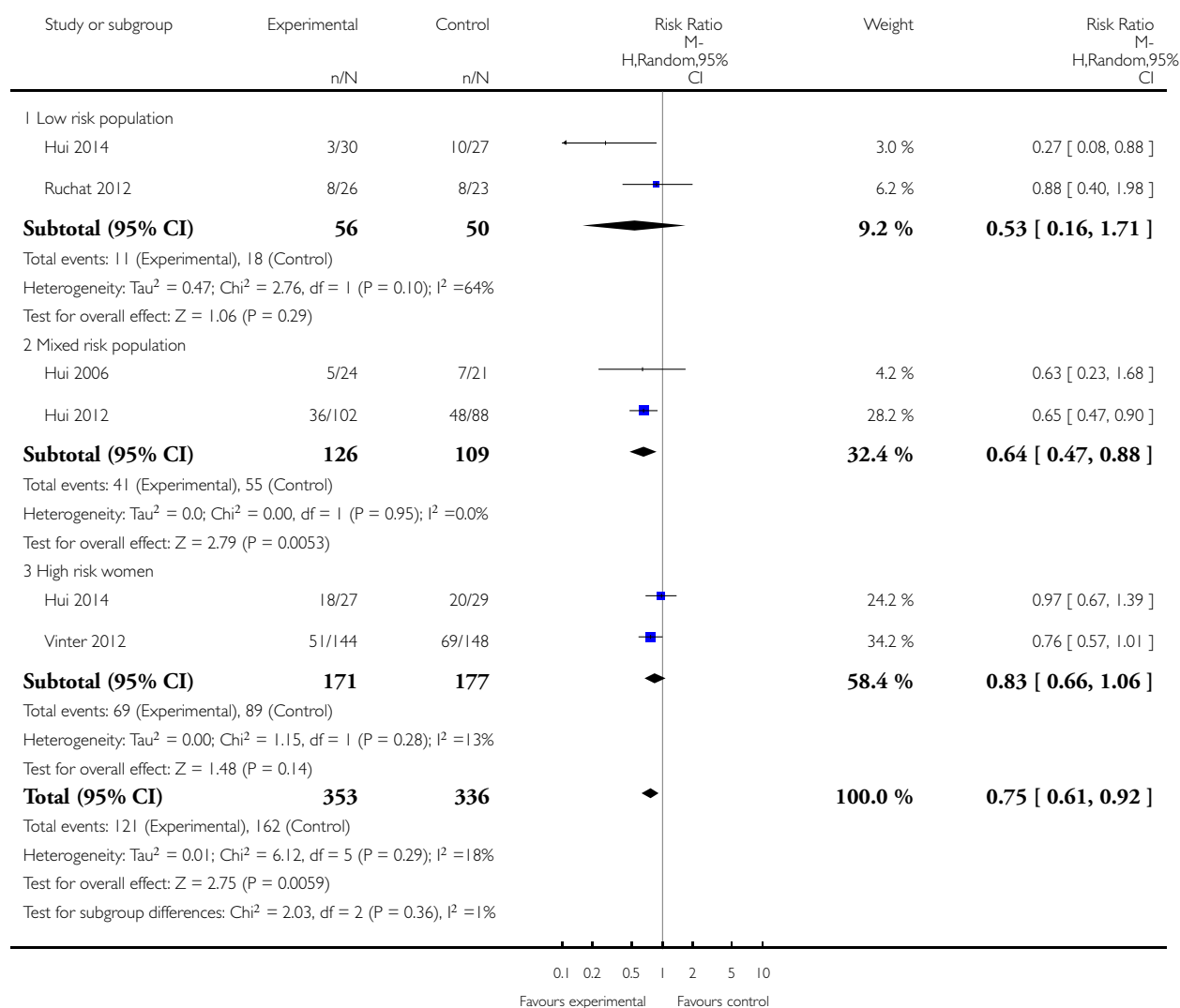


Analysis 5.1. Comparison 5 Diet and supervised exercise vs standard/other care, Outcome 1 Excessive weight gain.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 5 Diet and supervised exercise vs standard/other care

Outcome: 1 Excessive weight gain

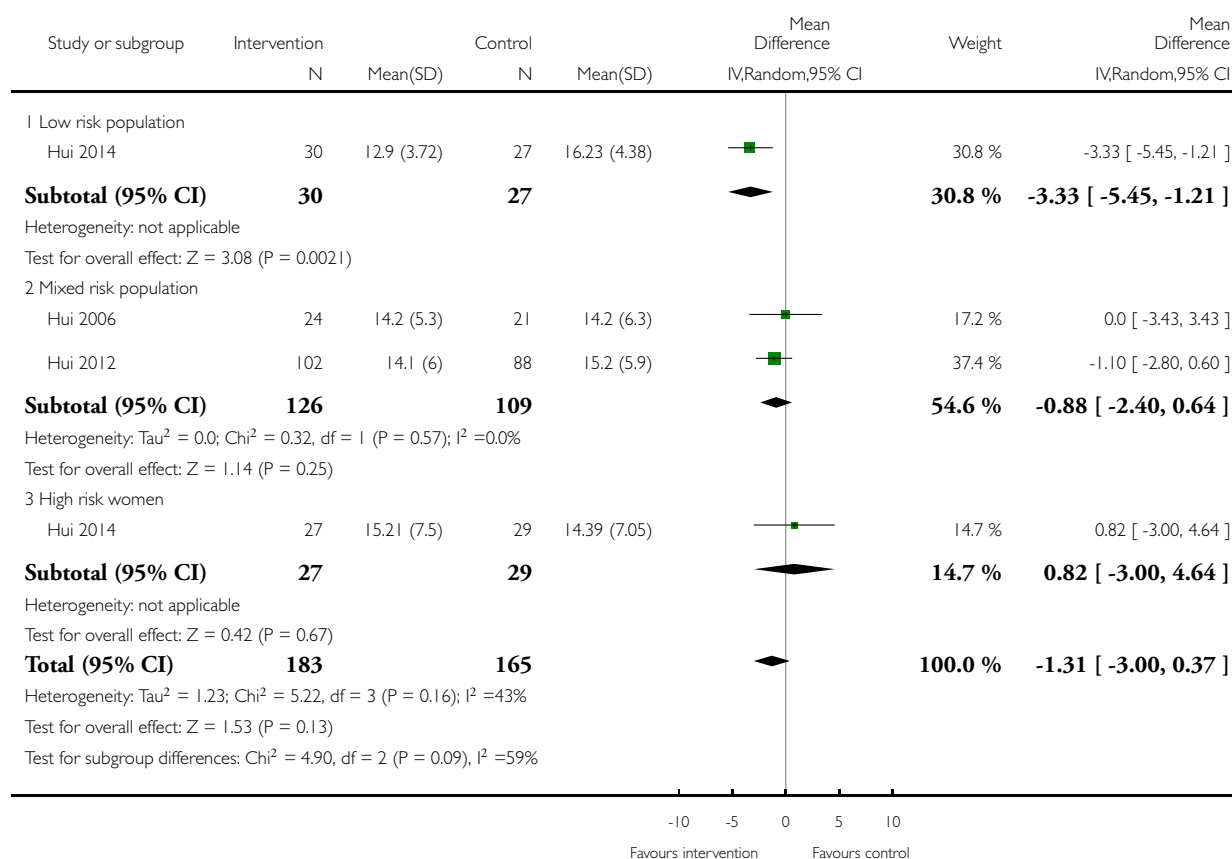


Analysis 5.2. Comparison 5 Diet and supervised exercise vs standard/other care, Outcome 2 Weight gain (kg).

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 5 Diet and supervised exercise vs standard/other care

Outcome: 2 Weight gain (kg)

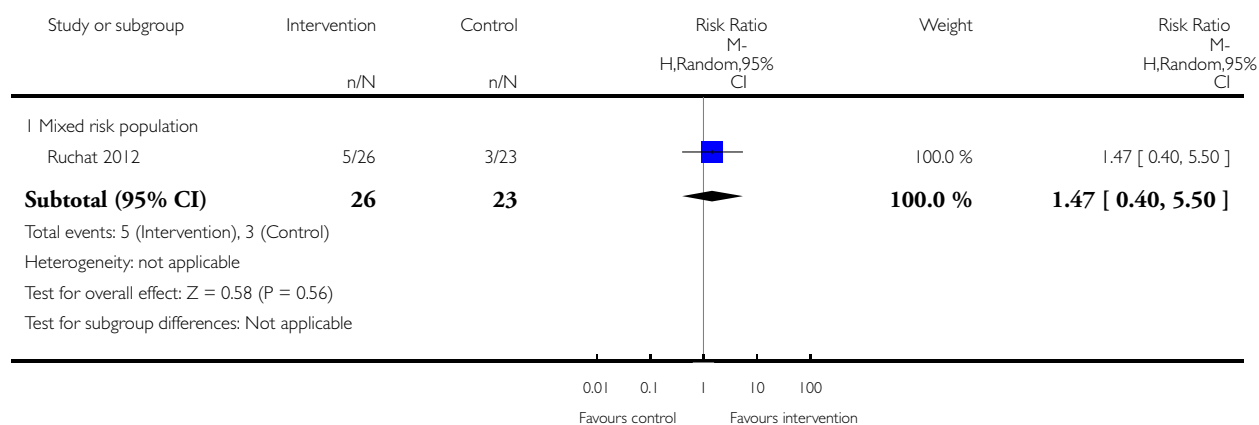


Analysis 5.3. Comparison 5 Diet and supervised exercise vs standard/other care, Outcome 3 Low weight gain.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 5 Diet and supervised exercise vs standard/other care

Outcome: 3 Low weight gain

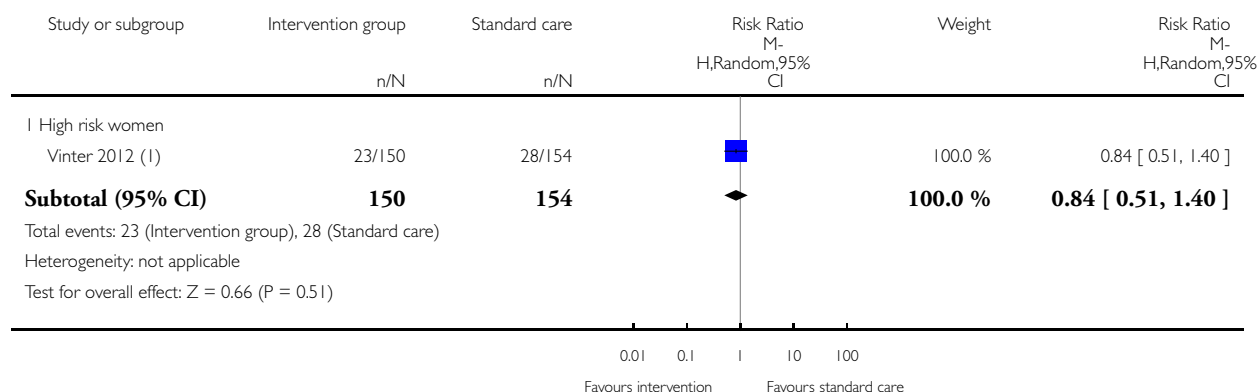


Analysis 5.4. Comparison 5 Diet and supervised exercise vs standard/other care, Outcome 4 Pre-eclampsia.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 5 Diet and supervised exercise vs standard/other care

Outcome: 4 Pre-eclampsia



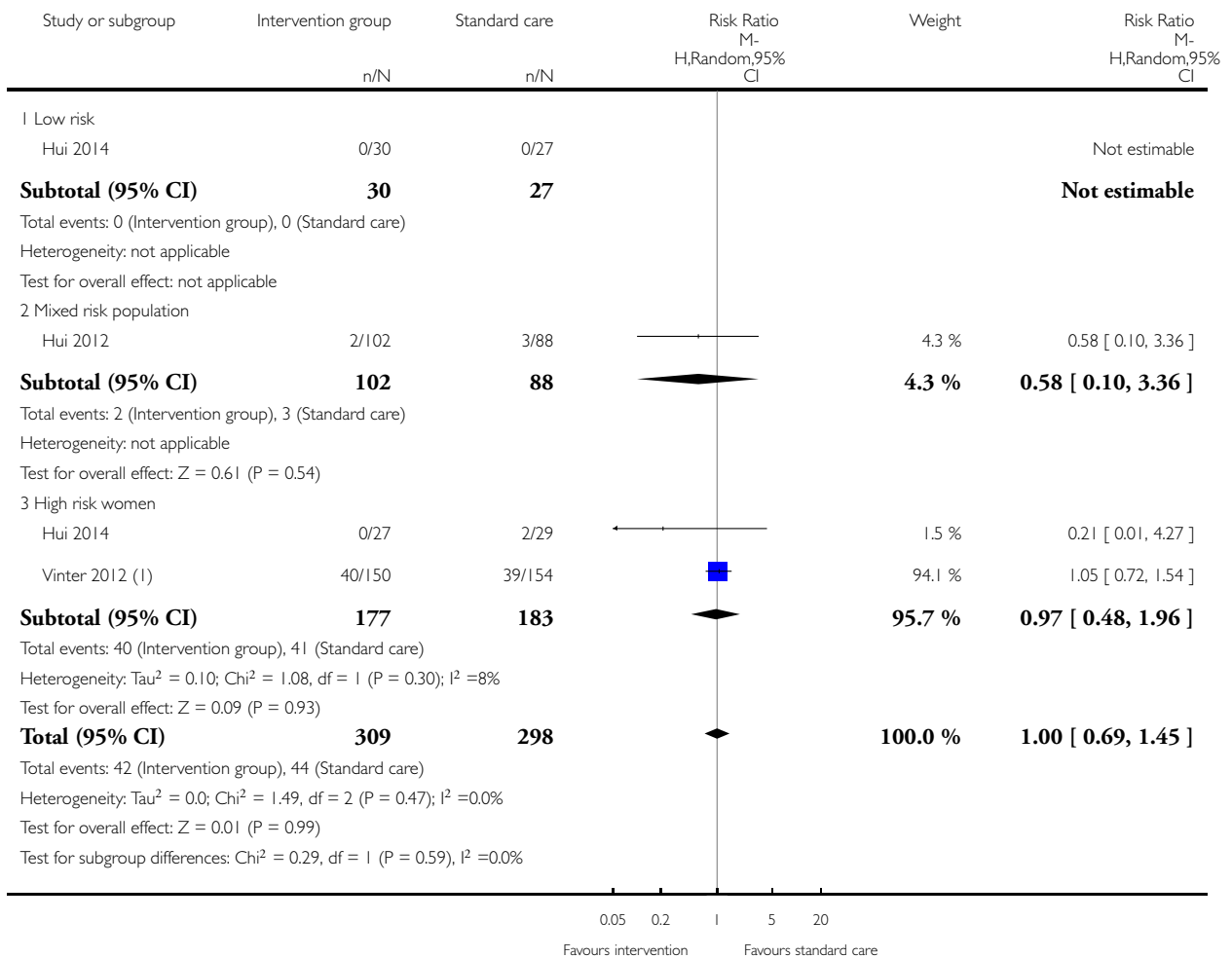
(I) PE/PI-H

Analysis 5.5. Comparison 5 Diet and supervised exercise vs standard/other care, Outcome 5 Caesarean delivery.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 5 Diet and supervised exercise vs standard/other care

Outcome: 5 Caesarean delivery



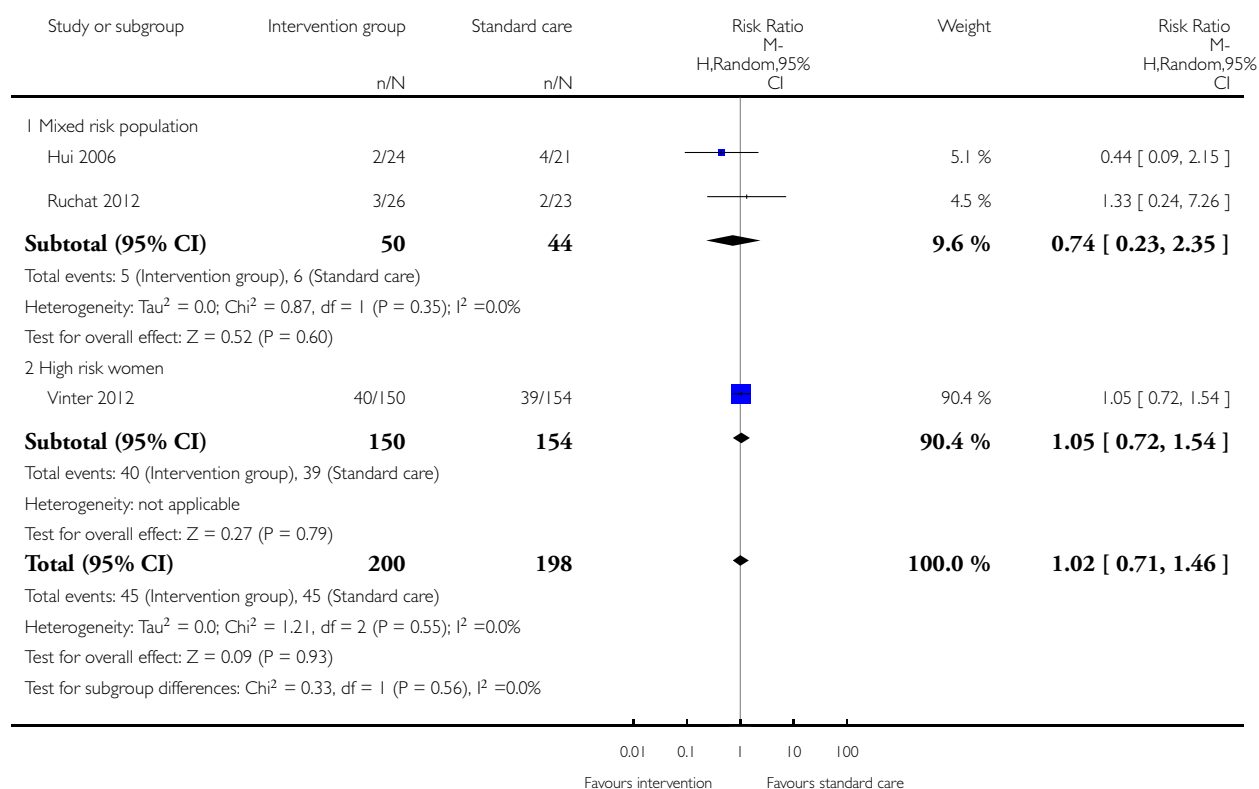
(I) obese women

Analysis 5.6. Comparison 5 Diet and supervised exercise vs standard/other care, Outcome 6 Macrosomia (Infant birthweight > 4000 g).

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 5 Diet and supervised exercise vs standard/other care

Outcome: 6 Macrosomia (Infant birthweight > 4000 g)

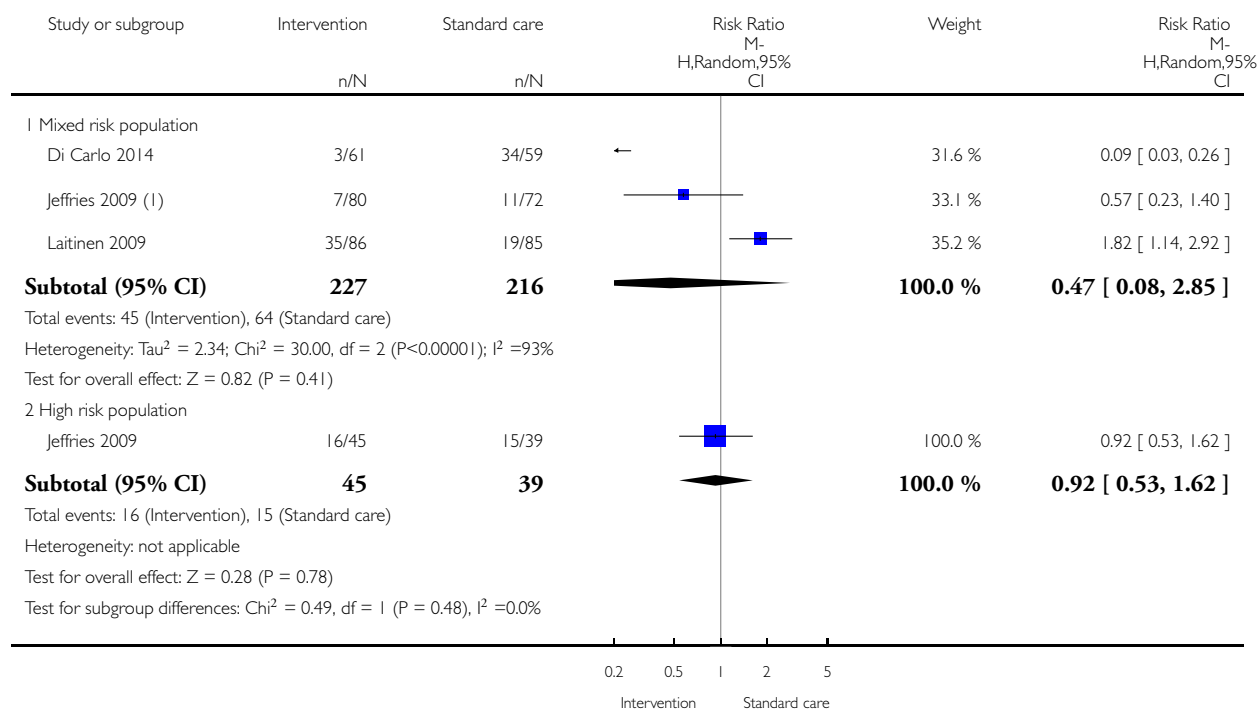


Analysis 6.1. Comparison 6 Diet counselling/other vs standard/other care, Outcome 1 Excessive weight gain.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 6 Diet counselling/other vs standard/other care

Outcome: 1 Excessive weight gain



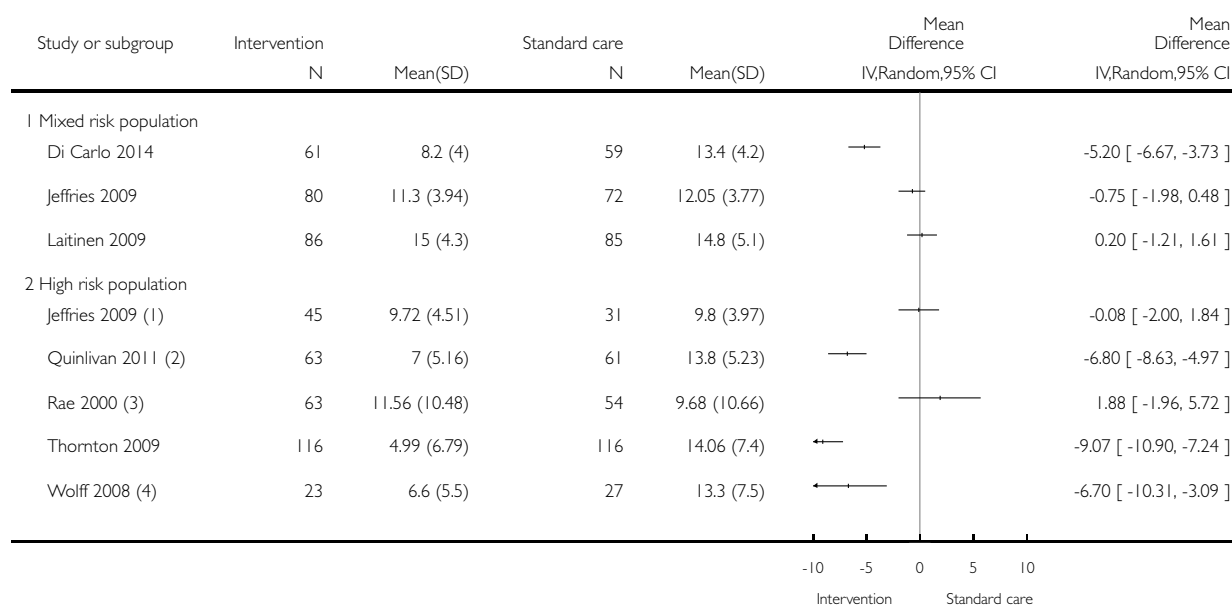
(1) included self-weighing

Analysis 6.2. Comparison 6 Diet counselling/other vs standard/other care, Outcome 2 Weight gain (kg).

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 6 Diet counselling/other vs standard/other care

Outcome: 2 Weight gain (kg)



(1) self-weighing intervention

(2) weight monitoring, counselling and continuity of care

(3) energy restriction diet counselling

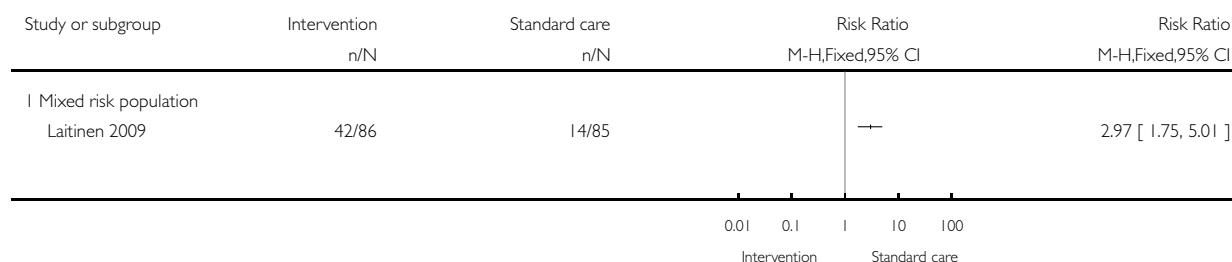
(4) energy-restriction diet counselling

Analysis 6.3. Comparison 6 Diet counselling/other vs standard/other care, Outcome 3 Low weight gain.

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 6 Diet counselling/other vs standard/other care

Outcome: 3 Low weight gain

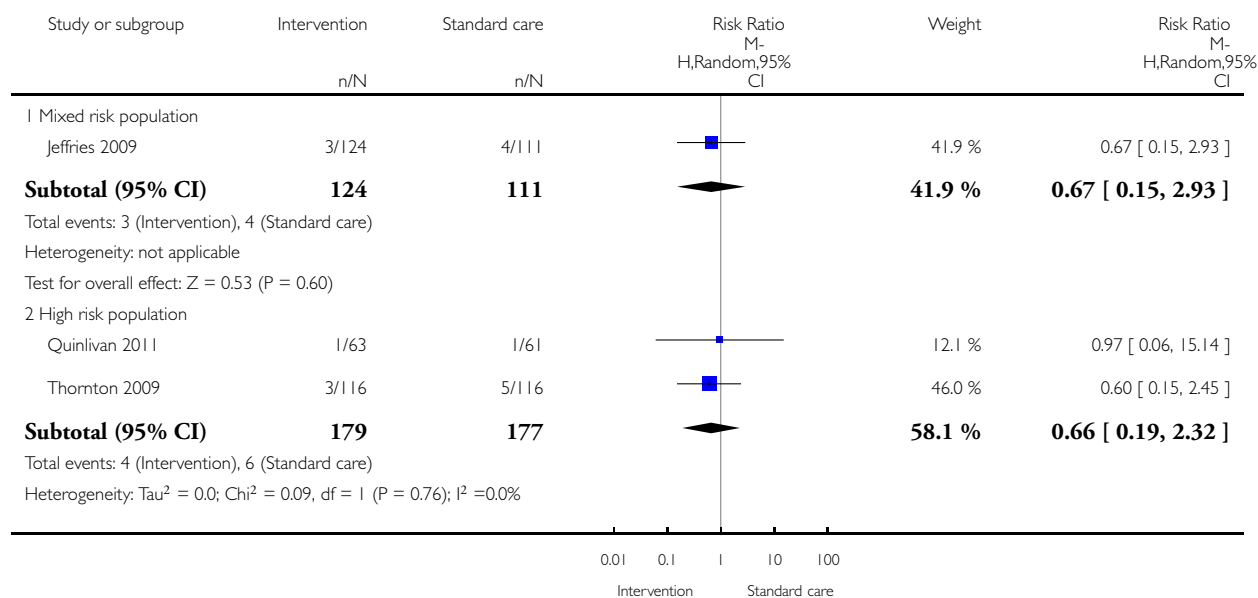


Analysis 6.4. Comparison 6 Diet counselling/other vs standard/other care, Outcome 4 Preterm birth.

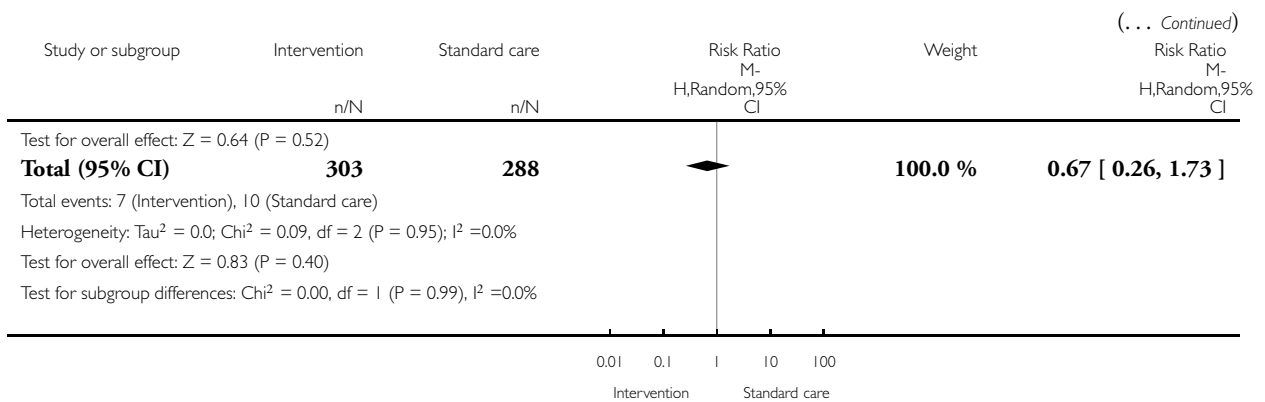
Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 6 Diet counselling/other vs standard/other care

Outcome: 4 Preterm birth



(Continued ...)

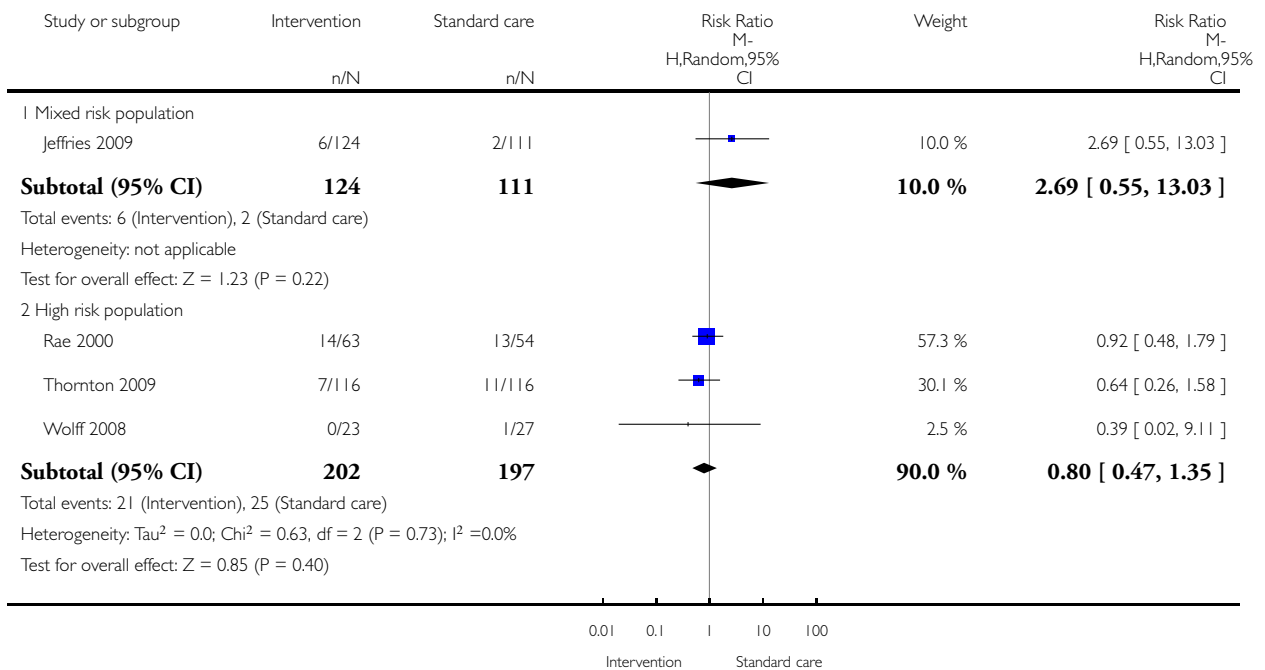


Analysis 6.5. Comparison 6 Diet counselling/other vs standard/other care, Outcome 5 Pre-eclampsia.

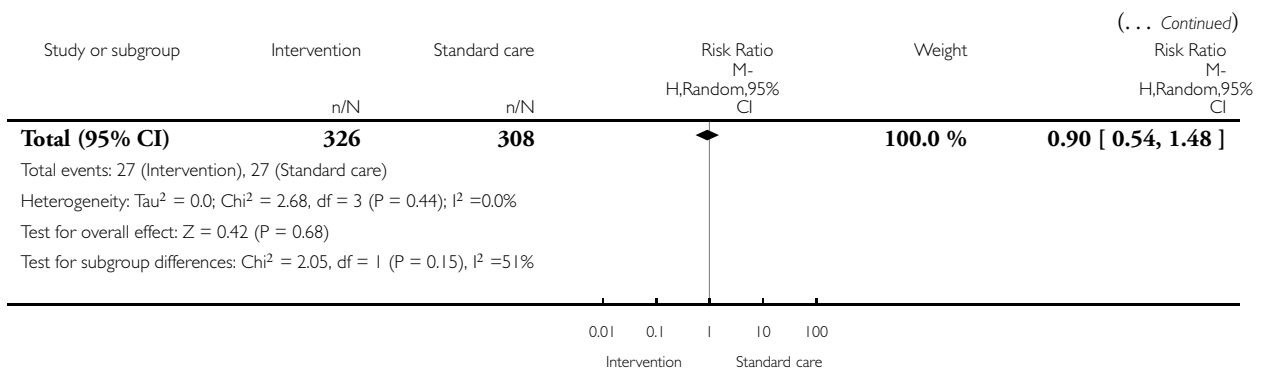
Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 6 Diet counselling/other vs standard/other care

Outcome: 5 Pre-eclampsia



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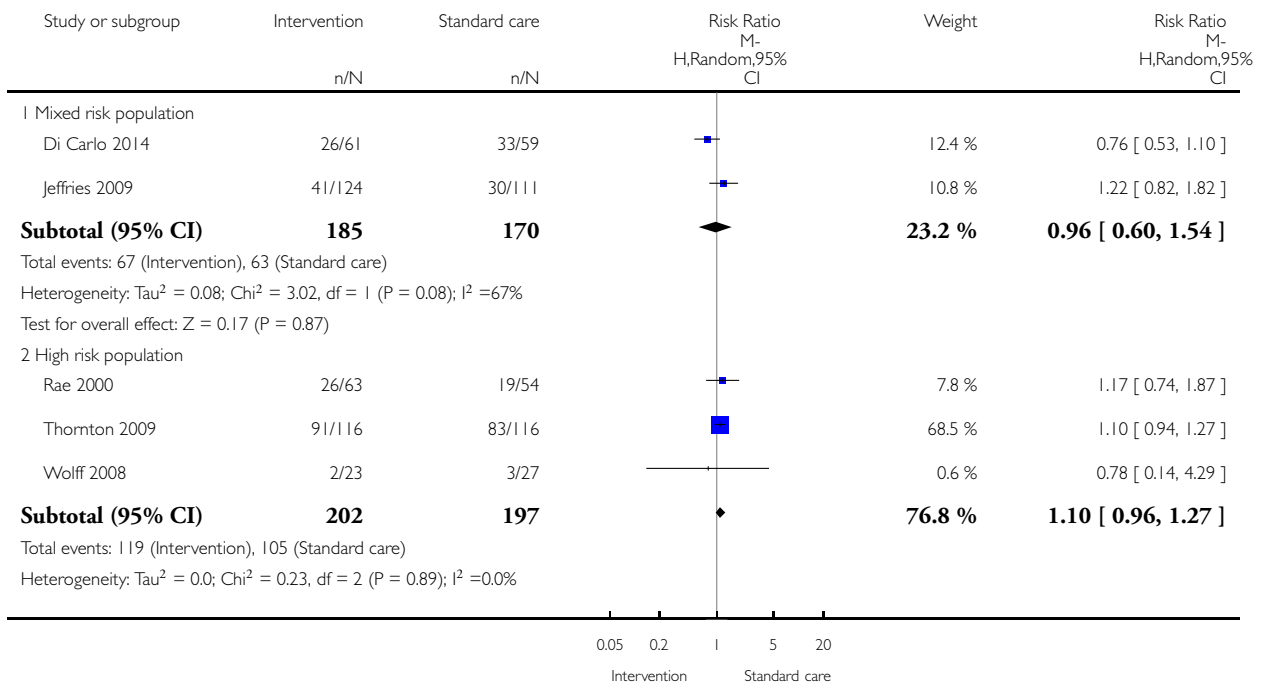


Analysis 6.6. Comparison 6 Diet counselling/other vs standard/other care, Outcome 6 Caesarean delivery.

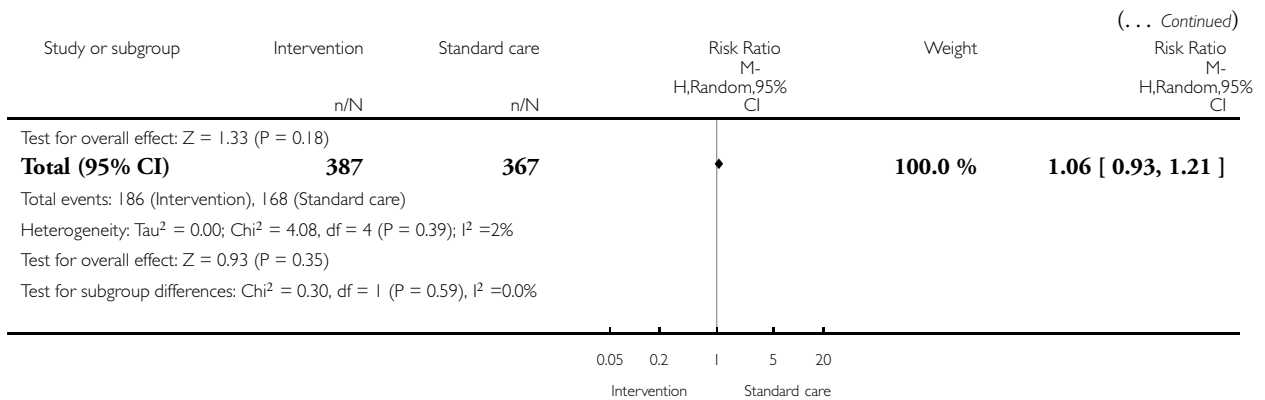
Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 6 Diet counselling/other vs standard/other care

Outcome: 6 Caesarean delivery



(Continued . . .)

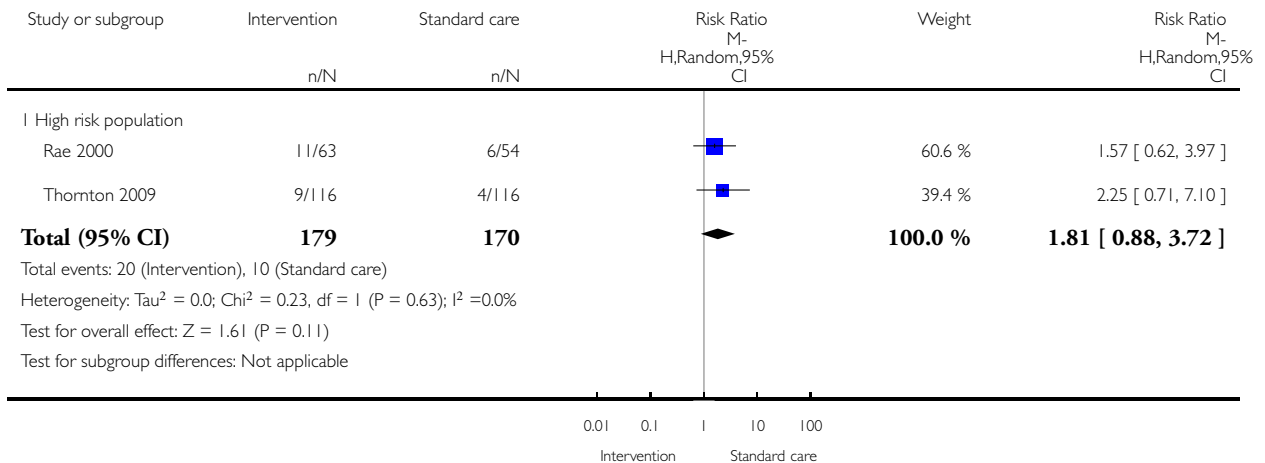


Analysis 6.7. Comparison 6 Diet counselling/other vs standard/other care, Outcome 7 Macrosomia (Infant birthweight > 4000 g).

Review: Diet or exercise, or both, for preventing excessive weight gain in pregnancy

Comparison: 6 Diet counselling/other vs standard/other care

Outcome: 7 Macrosomia (Infant birthweight > 4000 g)



ADDITIONAL TABLES

Table 1. Types of Interventions assessed in studies contributing data

Number	Study ID	Experimental intervention (unless otherwise stated, the control intervention was routine care)	Participants analysed	Contributed data		
				Low risk	Mixed risk	High risk
Diet counselling/other						
1	Di Carlo 2014	The intervention involved a supervised personalised diet plan meeting both personal preferences and specific gestational needs with the average caloric intake being 1916 kcal. The only fat allowed was olive oil. Participants in the intervention group underwent monthly follow-up appointments with a dietician who monitored their weight gain and discussed issues. Control group received standard brochure on healthy eating	120		/	
2.	Jeffries 2009	Women were given a personalised weight measurement card, advised of their optimal gestational weight gain based on their BMI at the time of recruitment and the	236		/	/

Table 1. Types of Interventions assessed in studies contributing data (Continued)

		United States IOM guidelines, and instructed to record their weight at 16, 20, 24, 28, 30, 32 and 34 weeks' gestation				
3.	Laitinen 2009	Dietary counselling was given by a dietitian at each study visit and aimed to modify dietary intake to conform with that currently recommended, particular attention being paid to the quality of dietary fat. Study visits took place 3 times during pregnancy and at 1, 6 and 12 months postpartum	171		/	
4.	Quinlivan 2011	This was a multifaceted intervention that included weighing on arrival and a brief dietary intervention by a food technologist at every antenatal visit. Other aspects of the intervention involved continuity of care provider and psychological assessment	124		/	
5.	Rae 2000	The intervention comprised instruction in a moderately energy	117		/	

Table 1. Types of Interventions assessed in studies contributing data (Continued)

		restricted diabetic diet providing between 1590-1776 kcal (70% RDA)				
6.	Thornton 2009	Participants were counselled in nutrition and monitored by a registered dietitian and given a detailed nutrition program similar to a diabetic diet	232			/
7.	Wolff 2008	Intervention comprise a healthy diet according to the official Danish dietary recommendations (% fat, protein, CHO, 30%, 15%-20%, 50%-55%). The energy intake was restricted based on individually estimated energy requirements and estimated energetic cost of fetal growth	50			/
Low GL diet						
8.	Clapp 2002b	Participants were randomised to either a low-glycaemic diet (aboriginal diet) or high-glycaemic diet (cafeteria diet)	20		/	
9.	Louie 2011	Intervention was a healthy low-GL diet of pro-	92			/

Table 1. Types of Interventions assessed in studies contributing data (Continued)

		tein (15%-25%) , fat (25%-30%) and carbohydrate (40%-45%) (ver- sus healthy high-fibre diet with moder- ate GL, similar to population aver- age). Participants attended at least 3 face-to-face vis- its with the study dietician for mon- itoring adherence and en- couragement. In- tervention began after 29th week				
10.	Moses 2009	Low-GL diet ver- sus high-GL diet. The dietary ad- vice by dietitian was individualised with specific men- tion of the en- ergy and nutrient balance to achieve normal weight gain during the 3rd trimester	63		/	
11.	Moses 2014	The intervention involved a low gly- caemic diet from 12 to 16 weeks' ges- tation for the re- mainder of preg- nancy (compared with conventional healthy eat- ing). Women re- ceived a detailed dietary education tailored for the group assignment at baseline - there	576		/	

Table 1. Types of Interventions assessed in studies contributing data (Continued)

		were no difference in the macronutrient distribution in the diets, only the substitution of carbohydrate-rich foods with low GL alternatives in the experimental group. Information booklets were provided. 4 contact points with a research dietitian were planned (first visit, phone call, midway and final visits) to collect data and ensure adherence				
12.	Rhodes 2010	Nutrition education, dietary counselling, and a low-GL diet (vs a low-fat diet)	50			/
13.	ROLO 2012	Low-GL dietary intervention given by a dietitian involving 1 dietary education session lasting 2 hours in groups of 2-6 women at baseline. Follow-up reinforcement sessions were held at 28 and 34 weeks' gestation. Women also received written resources about low-GL foods	759	/	/	/
Diet and exercise counselling						

Table 1. Types of Interventions assessed in studies contributing data (Continued)

14.	Althuisen 2013	The intervention involved counselling by members of the research team consisting of 5 x 15 minute sessions on weight, physical activity and diet. Interventions were face-to-face at 18, 22, 30, and 36 weeks' gestation, with a telephone session at 8 weeks post-partum. Counselors discussed how to control weight gain during and after pregnancy, and how to maintain a healthy lifestyle	219		/	/
15	Asbee 2009	At the initial visit, participants met with a registered dietician to receive a standardised counselling session, including information on pregnancy-specific dietary and lifestyle choices. Participants were instructed to engage in moderate-intensity exercise at least 3 times per week and preferably 5 times per week. Weight gain was reviewed at each routine antenatal visit	100		/	

Table 1. Types of Interventions assessed in studies contributing data (Continued)

16.	Asbee 2009	Comprehensive dietary and lifestyle intervention (counselling) (n = 1108) Intervention involved meetings and home visits with advice on dietary, exercise, and behavioural strategies delivered by a dietitian and trained research assistants. Exercise advice primarily encouraged women to increase their amount of walking and incidental activity	2212			/
17.	Ferrara 2011	Lifestyle intervention involved 3 in-person sessions and up to 15 telephone calls with counselling re diet, physical activity and breastfeeding up to 12 months postpartum. The intervention was delivered by 2 dietitians. Participants were encouraged to engage in moderate-intensity physical activity for 150 minutes per week and received written materials about food size, foods with low GL or low fat,	197			/

Table 1. Types of Interventions assessed in studies contributing data (Continued)

		and how to read food labels were discussed,				
18.	Guelinckx 2010	2 intervention arms: 1 involved a brochure only, the other involved a brochure and counselling by a trained nutritionist in 3 group sessions. A maximum of 5 women were brought together in these 1-hour sessions, which were scheduled at 15, 20, and 32 weeks of pregnancy. The sessions provided participants with recommendations on a balanced, healthy diet, and physical activity specifically designed for the study to limit weight gain	124			/
19.	Harrison 2013	Intervention provided dietary advice, simple healthy eating, and "physical activity messages" and weight gain self-monitoring. Also included "regular self-weighing as a key behavioural strategy"	203			/
20.	Hawkins 2014	A lifestyle intervention consisting of a culturally and	68			/

Table 1. Types of Interventions assessed in studies contributing data (Continued)

		lin- guistically modified, motivation- ally targeted, in- dividually tailored 6-month prenatal programme. Edu- cators encouraged women to achieve guidelines for physical activ- ity, decrease satu- rated fat and in- crease dietary fi- bre. The interven- tion consisted of 6 monthly in-per- son behavioural counselling ses- sions and 5 tele- phone booster ses- sions with follow- up to 6 weeks post- partum. Women were encourage to achieve ≥ 30 min- utes of moderate- intensity activity on most days of the week through walking and de- veloping a more active lifestyle				
21.	Huang 2011	The interven- tion was delivered at regularly sched- uled clinic vis- its by nurses with training in nutri- tion and physical fitness. The nurse discussed with each partic- ipant how to de- sign an individu- alised diet and physical	160		/	

Table 1. Types of Interventions assessed in studies contributing data (Continued)

		activity plan. The intervention consisted of 6 1-to-1 counselling sessions: 1 primary session (about 30-40 minutes) at the 16-week gestation visit, and 5 1-to-1 booster sessions (at 28 gestational weeks, 36-38 gestational weeks, before hospital discharge after a 3 to 7-day stay, 6 weeks' postpartum and 3 months postpartum). After each clinic visit, women in the experimental groups were sent a personalised graph of their weight changes. At the 1st session, the experimental groups also received a researcher-prepared brochure that provided detailed information on weight management goals during pregnancy and postpartum				
22.	Korpi-Hyovalti 2011	Individual dietary advice tailored to each participant at 6 visits to include a low fat diet rich in vegetables, fruit and berries. Moderate-intensity physical	60			/

Table 1. Types of Interventions assessed in studies contributing data (Continued)

		exercise was encouraged at 6 exercise counselling sessions				
23.	Luoto 2011	Individual counselling on physical activity and diet and weight gain. At the first visit the recommendations for gestational weight gain were discussed and an appropriate weight gain graph was selected to guide the participant in monitoring her weight gain. Physical activity counselling was implemented at 8-12 weeks' gestation and the dietary counselling session occurred at 16-18 weeks' gestation. Physical activity counselling was enhanced at 4, and diet counselling at 3 subsequent visits	399			/
24.	Petrella 2013	Lifestyle intervention involving a caloric restricted diet (1500 kcal/day) and mild exercise 30 minutes/day, 3 times per week monitored by a pedometer	63			/
25.	Phelan 2011	The Fit for Delivery intervention included	401	/		/

Table 1. Types of Interventions assessed in studies contributing data (Continued)

		a face-to-face visit with an interventionist at the onset of treatment who discussed appropriate weight gains during pregnancy, physical activity (30 minutes of walking most days of the week), and calorie goals (20 kcal/kg). Emphasis was placed on decreasing high fat foods, increasing physical activity, and daily self-monitoring. Women also received personalised weight graphs after each clinic visit, automated supportive postcards and 3 supportive phone calls				
26.	Polley 2002	Intervention conducted at routine clinic visits by staff with training in nutrition or psychology involved education about weight gain, healthy eating, and exercise, and individual graphs of their weight gain. After each clinic visit, women were sent a personalised graph of their weight gain	110	/		/

Table 1. Types of Interventions assessed in studies contributing data (Continued)

27.	Poston 2013	A lifestyle intervention (diet plus exercise) involving 1 1-to-1 counselling session with a health trainer and then weekly group sessions for 8 consecutive weeks from 19 weeks' gestation. Sessions delivered by health trainers involved diet and exercise advice informed by psychological models of health behaviour. Dietary advice focused on increased consumption of foods with a low-dietary GL, and reduction of saturated fats. Physical activity advice encouraged women to increase daily walking activity at moderate-intensity level, setting goals monitored by a pedometer. Women also received a DVD of a pregnancy specific exercise regimen	154			/
28.	Renault 2014	A 3-arm study with 2 intervention groups. 1 intervention involved unsupervised exercise only (women were	389			/

Table 1. Types of Interventions assessed in studies contributing data (Continued)

		given a pedometer), the other involved diet and exercise counselling only. The diet and exercise intervention included follow-up on a hypocaloric Mediterranean-style diet. Instruction was given by a dietician every 2 weeks with alternating outpatient visits and phone calls, including weight measurement, encouragement and correcting advice on exercise and diet				
29.	Vesco 2013	Intervention involved a 45-minute diet consultation with an individualised caloric goal, a second individualised session, weekly group meetings with weigh ins, food/activity logs. Women are encouraged to accumulate at least 30 minutes of moderate-intensity activity per day. Pedometers recorded steps with a target of 10,000 steps daily and were only provided to the intervention group	114			/

Table 1. Types of Interventions assessed in studies contributing data (Continued)

Unsupervised exercise intervention						
30.	Kong 2014	Unsupervised exercise intervention involved a walking program on treadmill or other setting for a minimum of 150 min/week. Women were loaned treadmills for the study and steps monitored	42			/
31.	Renault 2014	A 3-arm study with 2 intervention groups. 1 intervention involved unsupervised exercise only (women were given a pedometer), the other involved diet and exercise counselling. The physical activity intervention included encouragement or increase physical activity, aiming at a daily step count of 11,000, monitored by pedometer assessment on 7 consecutive days, every 4 weeks	389			/
32.	Ronnberg 2014	Intervention involved prescribed exercise to be at a "moderate level of exertion for approximately 30 min/day"	374	/	/	/

Table 1. Types of Interventions assessed in studies contributing data (Continued)

Supervised exercise intervention						
33.	Barakat 2011	Intervention involved 35- to 45-minute exercise sessions 3 times per week from the start of the pregnancy (weeks 6-9) to the end of the 3rd trimester (weeks 38-39) - an average of 85 training sessions. Exercise intensity was light-to-moderate and was supervised by a fitness specialist in groups of 10-12 women	80		/	
34.	Cordero 2014	A supervised exercise program consisting of aerobic and toning exercises for 3 sessions per week. 2 weekly sessions were performed on land (60 minutes) and 1 session was aquatic based (50 minutes). Program commenced from 10-14 weeks to the end of the third trimester. Sessions were supervised by a qualified fitness specialist and an obstetrician	257		/	
35.	De Oliveria Melo 2012	Supervised moderate-intensity exercise (initiated at 13 weeks or 20	187		/	

Table 1. Types of Interventions assessed in studies contributing data (Continued)

		weeks) vs control . Sessions consisted of warming up and stretching exercises, followed by supervised walking 3 times a week in the open air. Supervised by physical education professionals and medical, physiotherapy and nursing students				
36.	Haakstad 2011	Exercise (60 minutes supervised aerobic dance at least twice a week for a minimum of 12 weeks) (n = 52). Women in the exercise group were advised to have moderate, self-imposed physical activity on the remaining weekdays	105		/	
37.	Murtezani 2014	The exercise training program started in the second trimester and was continued until the end of pregnancy. Each session consisted of 40-45 minutes of aerobic and strength exercise. Individuals were supervised by certified aerobic-instructors, and each session included a maxi-	63		/	

Table 1. Types of Interventions assessed in studies contributing data (Continued)

		mum of 10 participants. Intensity was moderate-to-vigorous; supine postures and Valsalva manoeuvres were avoided				
38.	Nascimento 2012	Intervention consisted of a supervised exercise program guided by a trained physical therapist in weekly classes with light-to-moderate-intensity exercise for 40 minutes. It also included home exercise counselling which was to be performed 5 times per week (consisting of a sequence of 22 exercises or walking)	82			/
39.	Oostdam 2012	A supervised exercise intervention comprising 2 sessions of aerobic and strengthening exercises per week; each exercise session lasted for 60 minutes from 20 weeks' gestation	101			/
40.	Petrov Fieril 2014	Intervention group received supervised resistance exercise twice a week, with light barbells and weight plates in a group setting, performed at an ac-	72			/

Table 1. Types of Interventions assessed in studies contributing data (Continued)

		tivity level equivalent to within moderate-to-vigorous between weeks 14 to 25 gestation, and was self-adjusted. In addition, walking, cycling, water-gymnastics, Pilates, yoga and home exercises that included pelvic floor training were recommended				
41.	Price 2012	Intervention involved a program of supervised aerobic training of 45-60 minutes, 4 days per week	62		/	
42.	Ruiz 2013	Intervention involved light-to moderate-intensity supervised aerobic and resistance exercises (including pelvic floor exercises) performed 3 days a week (50-55 minutes per session) from 9 weeks to weeks 38-39. Exercise sessions involved 8-10 participants	962	/	/	/
43	Santos 2005	The intervention consisted of a program of supervised physical exercise of 60 minutes duration, performed 3 times	72			/

Table 1. Types of Interventions assessed in studies contributing data (Continued)

		per week for 12 weeks				
44.	Stafne 2012	intervention comprised a 12-week regular standardised exercise program including aerobic activity, strength training, and balance exercises. The exercise program followed standard recommendations and included moderate-intensity to high-intensity activity 3 or more days per week. Physiotherapist-supervised training sessions of 60 minutes in groups of 8-15 women were offered once per week	702		/	
Supervised exercise and diet intervention						
45.	Hui 2006	Exercise intervention involved a weekly supervised group session including floor aerobics, stretching and strength exercises, and similar home-based exercise 3-5 times/week for 30-45 minutes per session. A video was provided to participants to assist with home-based exercise. Diet inter-	46		/	

Table 1. Types of Interventions assessed in studies contributing data (Continued)

		vention involved a computer-assisted food choice map interview and a personalised plan by a dietician				
46.	Hui 2012	Exercise intervention involved an exercise regimen comprising 3 to 5 times per week, including a weekly supervised community-based session and multiple home sessions, of mild-to-moderate exercise for 30 to 45 minutes. Program started between 20-26 weeks. Group exercise sessions including aerobics were held in community centres and instructors were licensed fitness trainers. 2 dietary interviews with counselling were provided	190		/	
47.	Hui 2014	Lifestyle intervention (diet counselling and a supervised exercise program) vs control. Intervention included "a community-based exercise program specifically designed for pregnant women was provided". An exercise regimen, 3	113		/	/

Table 1. Types of Interventions assessed in studies contributing data (Continued)

		to 5 times per week including a weekly exercise session and home sessions with DVD instruction of mild-to-moderate aerobic exercise for 30 to 45 minutes was recommended. Program started between 20-26 weeks and continued to 36 weeks. Group exercise sessions including aerobics were held in community centres and instructors were licensed fitness trainers. 2 dietary interviews with dietician counselling using a Food Choice Map were provided (baseline and 2 months later) . Control group received standard care				
48.	Ruchat 2012	Moderate-intensity exercise 3-4 times per week, including 1 supervised session (versus low-intensity exercise in the form of a walking program 3-4 times per week). All participants received a diet plan based on a modified diabetic diet	49		/	

Table 1. Types of Interventions assessed in studies contributing data (Continued)

49.	Vinter 2012	A lifestyle intervention consisting of dietary counselling and exercise. The intervention involved dietary advice on 4 occasions (15, 20, 28 and 35 weeks) by a dietician. Energy requirements were personalised for each participant. Exercise intervention included a pedometer and free gym membership for 6 months. Participants were encouraged to do 30-60 minutes moderate-physical activity daily. In addition, at the gym they had 1 supervised aerobic class with a physiotherapist for 1 hour each week	304			/

BMI: body mass index

CHO: carbohydrate

GL: glycaemic load

IOM: Institute of Medicine

RDA: recommended dietary allowance

APPENDICES

Appendix I. Adjusted data for Luoto 2011

Continuous outcome	Intervention (Original data) (Total number = 216)		Control (Original data) (Total number = 179)		M ¹	ICC ²	Design effect ³	Adjusted sample ⁴ sizes	
	Cluster number	$\bar{x} \pm SD$	Cluster number	$\bar{x} \pm SD$				Intervention	Control
Maternal weight gain	7	13.8±5.8	7	14.2±5.1	28.21	0.12	4.27	50.64	41.96

1 M = average cluster size = ((total number of intervention + total number of control)/(cluster number of intervention + cluster number of control))

2 ICC = intraclass correlation; obtained from the reliable external source (Luoto 2010).

3 Design effect = 1 + (M-1)ICC

4 Adjusted sample sizes = n / design effect

Dichotomous outcomes	Intervention (Original data) (Total number = 216, cluster number = 7)	Control (Original data) (Total number = 179, cluster number = 7)	M ¹	ICC ²	Design effect ³	Intervention (Adjusted data) ⁴		Control (Adjusted data) ⁴	
	n	n				Total N	n	Total N	n
Pre-eclampsia	14	10	28.21	0.12	4.27	50.64	3.28	41.96	2.34
Birth-weight > 4000 g	37	36	28.21	0.12	4.27	50.64	8.67	41.96	8.44
Infant birth-weight > 90th centile	26	34	28.21	0.12	4.27	50.64	6.10	41.96	7.97

(Continued)

In-fant birth-weight < the 10th centile	10	5	28.21	0.12	4.27	50.64	2.34	41.96	1.17

Appendix 2. Data for Rauh 2013

Continuous outcomes	Intervention		Control		Adjusted P value
	$\bar{x} \pm \text{SD}$	Total number	$\bar{x} \pm \text{SD}$	Total number	
Weight gain	14.1 $\pm$ 4.1	152	15.6 $\pm$ 5.8	74	0.035
Weight retention (at 4 months post-partum)	2.1 $\pm$ 4.3	152	3.3 $\pm$ 5.1	72	0.070
Infant birthweight	3406 $\pm$ 402	156	3414 $\pm$ 445	79	-

Dichotomous outcomes	Intervention		Control		Adjusted P value
	Number	Total number	Number	Total number	
Excessive weight gain	58	152	44	74	0.032
Low weight gain	32	152	14	74	0.972
Weight retention (> 5 kg)	26	152	22	72	0.034
Preterm	4	156	5	79	0.088
Caesarean delivery	47	156	33	79	0.145
Gestational diabetes	8	156	9	79	0.183
Infant birthweight > 90th centile	10	156	7	79	0.702
Infant birthweight < 10th centile	6	156	3	79	0.990

(Continued)

Induction of labour	40	156	29	79	0.191

WHAT'S NEW

Last assessed as up-to-date: 5 November 2014.

Date	Event	Description
12 June 2015	Amended	Minor correction to acknowledgements.

HISTORY

Protocol first published: Issue 2, 2008

Review first published: Issue 4, 2012

Date	Event	Description
23 April 2015	New citation required and conclusions have changed	High-quality evidence suggests that diet or exercise, or both, interventions are effective in reducing excessive gestational weight gain. Hypertension, caesarean delivery, macrosomia and neonatal respiratory distress may also be reduced, particularly with combined diet and exercise interventions. Exercise appears to be an important part of controlling weight gain in pregnancy and more research is needed to establish safe guidelines
5 November 2014	New search has been performed	Search updated and 169 new records identified. There are now 65 (previously 28) included studies, 49 (previously 27) of which contribute data The title has been changed from 'Interventions for preventing excessive weight gain during pregnancy' to ' <i>Diet or exercise, or both</i> , for preventing excessive weight gain during pregnancy'. This was done to limit the otherwise enormous scope of the review. As a result of the title modification, two previously included 1970s studies of (obsolete) appetite suppressant drug interventions were excluded in this update. Drug interventions (e.g. metformin, probiotics), will now need to be addressed under a separate title Methods updated and GRADE 'Summary of findings'

(Continued)

		tables have been incorporated
10 November 2008	Amended	The <i>Types of interventions</i> section was amended by the inclusion of the phrase 'or other interventions for preventing excessive weight gain in pregnancy'. This amendment was made to ensure that the selection criteria are consistent with the objectives of the review which are to evaluate the effectiveness of all interventions (or combinations of interventions) to prevent excessive weight gain

CONTRIBUTIONS OF AUTHORS

B Muktabhant (BM) conceived and designed the draft protocol. P Lumbiganon (PL) and C Ngamjarus (CN) reviewed and commented on the revisions of the protocol. For the original review, BM, CN and T Dowswell (TD) selected studies, extracted data and conducted data analysis. BM and TD drafted the original review with feedback from PL and CN. For the update, BM and T Lawrie (TL) selected studies, extracted data, conducted data analysis and prepared the review. ML and PL contributed to data analysis, discussion and revision of the manuscript. All authors approved the final version of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Khon Kaen University, Thailand.
- University of Liverpool, UK.

External sources

- Thai Cochrane Network, Thailand.
- Thailand Research Fund/Distinguished Professor Award, Thailand.
- UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research (RHR), World Health Organization, Switzerland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This update differs from the protocol and previous versions of the review in the following ways.

1. The title has been changed from 'Interventions for preventing excessive weight gain during pregnancy' to '*Diet or exercise, or both, for preventing excessive weight gain during pregnancy*'. This was done to limit the otherwise enormous scope of the review. As a result of the title modification, two previously included 1970s studies of (obsolete) appetite suppressant drug interventions were excluded in this update. Drug interventions (e.g. metformin, probiotics), will now need to be addressed under a separate title.
2. The protocol and previous versions of this review included quasi-RCTs. For this update, we have excluded quasi-RCTs. We believe that the large and growing number of RCTs in this field justifies our approach of only using the best quality trials (RCTs).
3. We amended the [Subgroup analysis and investigation of heterogeneity](#) section of the methods by including subgroup analysis according to the risk of excess weight-related adverse outcomes (low-risk, mixed-risk and high-risk populations).
4. For this update, we decided to include the additional outcomes 'birthweight' and 'hypertension'; these are frequently reported outcomes in the context of the review interventions. Although they were not prespecified, the decision to include these outcomes was taken before commencing data extraction. We re-visited previously included studies to retrieve these data, where reported. By capturing these additional data we hope that this and future versions of the review will be more complete.
5. We amended the outcome 'complications relating to macrosomia' to include 'neonatal respiratory distress syndrome'.

INDEX TERMS

Medical Subject Headings (MeSH)

*Diet; *Exercise; *Weight Gain; Counseling; Overweight [complications; *prevention & control]; Pregnancy Complications [*prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Infant, Newborn; Pregnancy



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Interventions for treating constipation in pregnancy (Review)

Rungsiprakarn P, Laopaiboon M, Sangkomkamhang US, Lumbiganon P, Pratt JJ

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	3
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	4
BACKGROUND	7
OBJECTIVES	10
METHODS	10
RESULTS	14
Figure 1.	15
Figure 2.	17
Figure 3.	18
ADDITIONAL SUMMARY OF FINDINGS	20
DISCUSSION	23
AUTHORS' CONCLUSIONS	23
ACKNOWLEDGEMENTS	24
REFERENCES	24
CHARACTERISTICS OF STUDIES	26
DATA AND ANALYSES	32
Analysis 1.1. Comparison 1 Stimulant laxatives versus bulk-forming laxatives, Outcome 1 Improvement in constipation.	33
Analysis 1.2. Comparison 1 Stimulant laxatives versus bulk-forming laxatives, Outcome 2 Abdominal discomfort.	33
Analysis 1.3. Comparison 1 Stimulant laxatives versus bulk-forming laxatives, Outcome 3 Diarrhoea.	34
Analysis 1.4. Comparison 1 Stimulant laxatives versus bulk-forming laxatives, Outcome 4 Women's satisfaction.	35
Analysis 2.1. Comparison 2 Stimulant laxatives versus bulk-forming laxatives (Sensitivity analysis: Senokot and Normax data separated), Outcome 1 Improvement in constipation.	36
Analysis 2.2. Comparison 2 Stimulant laxatives versus bulk-forming laxatives (Sensitivity analysis: Senokot and Normax data separated), Outcome 2 Abdominal discomfort.	37
Analysis 2.3. Comparison 2 Stimulant laxatives versus bulk-forming laxatives (Sensitivity analysis: Senokot and Normax data separated), Outcome 3 Diarrhoea.	38
Analysis 2.4. Comparison 2 Stimulant laxatives versus bulk-forming laxatives (Sensitivity analysis: Senokot and Normax data separated), Outcome 4 Women's satisfaction (rated as good or acceptable).	39
Analysis 3.1. Comparison 3 Fibre supplementation versus no intervention, Outcome 1 Frequency of stools (per week).	40
ADDITIONAL TABLES	40
APPENDICES	40
WHAT'S NEW	41
CONTRIBUTIONS OF AUTHORS	41
DECLARATIONS OF INTEREST	41
SOURCES OF SUPPORT	41
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	42
INDEX TERMS	42

Interventions for treating constipation in pregnancy

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ABSTRACT

Background

Constipation is a common symptom experienced during pregnancy. It has a range of consequences from reduced quality of life and perception of physical health to haemorrhoids. An understanding of the effectiveness and safety of treatments for constipation in pregnancy is important for the clinician managing pregnant women.

Objectives

To assess the effectiveness and safety of interventions (pharmacological and non-pharmacological) for treating constipation in pregnancy.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 April 2015), ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) (30 April 2015) and reference lists of retrieved studies.

Selection criteria

We considered all published, unpublished and ongoing randomised controlled trials (RCTs), cluster-RCTs and quasi-RCTs, evaluating interventions (pharmacological and non-pharmacological) for constipation in pregnancy. Cross-over studies were not eligible for inclusion in this review. Trials published in abstract form only (without full text publication) were not eligible for inclusion.

We compared one intervention (pharmacological or non-pharmacological) against another intervention, placebo or no treatment.

Data collection and analysis

Two review authors independently assessed trials for inclusion and risk of bias, extracted data and checked them for accuracy.

Main results

Four studies were included, but only two studies with a total of 180 women contributed data to this review. It was not clear whether they were RCTs or quasi-RCTs because the sequence generation was unclear. We classified the overall risk of bias of three studies as moderate and one study as high risk of bias. No meta-analyses were carried out due to insufficient data.

There were no cluster-RCTs identified for inclusion. Comparisons were available for stimulant laxatives versus bulk-forming laxatives, and fibre supplementation versus no intervention. There were no data available for any other comparisons.

During the review process we found that studies reported changes in symptoms in different ways. To capture all data available, we added a new primary outcome (improvement in constipation) - this new outcome was not prespecified in our published protocol.

Stimulant laxatives versus bulk-forming laxatives

No data were identified for any of this review's prespecified primary outcomes: pain on defecation, frequency of stools and consistency of stools.

Compared to bulk-forming laxatives, pregnant women who received stimulant laxatives (Senokot or Normax) had an improvement in constipation (risk ratio (RR) 1.59, 95% confidence interval (CI) 1.21 to 2.09; 140 women, one study, *moderate quality of evidence*), but also had more abdominal discomfort (RR 2.33, 95% CI 1.15 to 4.73; 140 women, one study, *low quality of evidence*), and a borderline difference in diarrhoea (RR 4.50, 95% CI 1.01 to 20.09; 140 women, one study, *moderate quality of evidence*). In addition, there was no clear difference in women's satisfaction (RR 1.06, 95% CI 0.77 to 1.46; 140 women, one study, *moderate quality of evidence*).

One of the stimulant laxatives, Normax (dioctyl sodium sulphosuccinate and dihydroxy anthraquinone) is no longer used for the treatment of constipation in pregnant women (and the [package information](#) advises that it should not be used during pregnancy or breastfeeding). We therefore carried out a non-prespecified sensitivity analysis with the data for Senokot and Normax presented separately. Results for Senokot and Normax were very similar, thus results for the individual drugs largely reflected findings for the combined analysis, although when individual drugs were compared with bulk-forming laxatives there was no longer a clear difference between groups in terms of abdominal discomfort and diarrhoea.

No usable data were identified for any of this review's secondary outcomes: quality of life; dehydration; electrolyte imbalance; acute allergic reaction; or asthma.

Fibre supplementation versus no intervention

Pregnant women who received fibre supplementation had a higher frequency of stools compared to no intervention (mean difference (MD) 2.24 times per week, 95% CI 0.96 to 3.52; 40 women, one study, *moderate quality of evidence*). Fibre supplementation was associated with improved stool consistency as defined by trialists (hard stool decreased by 11% to 14%, normal stool increased by 5% to 10%, and loose stool increased by 0% to 6%).

No usable data were reported for either the primary outcomes of pain on defecation and improvement in constipation or any of this review's secondary outcomes as listed above.

Quality

Five outcomes were assessed with the GRADE software: improvement in constipation, frequency of stools, abdominal discomfort, diarrhoea and women's satisfaction. These were assessed to be of moderate quality except for abdominal discomfort which was assessed to be of low quality. The results should therefore be interpreted with caution. There were no data available for evaluation of pain on defecation or consistency of stools.

Authors' conclusions

There is insufficient evidence to comprehensively assess the effectiveness and safety of interventions (pharmacological and non-pharmacological) for treating constipation in pregnancy, due to limited data (few studies with small sample size and no meta-analyses). Compared with bulk-forming laxatives, stimulant laxatives appear to be more effective in improvement of constipation (*moderate quality evidence*), but are accompanied by an increase in diarrhoea (*moderate quality evidence*) and abdominal discomfort (*low quality evidence*) and no difference in women's satisfaction (*moderate quality evidence*). Additionally, fibre supplementation may increase frequency of stools compared with no intervention (*moderate quality evidence*), although these results were of moderate risk of bias.

There were no data for a comparison of other types of interventions, such as osmotic laxatives, stool softeners, lubricant laxatives and enemas and suppositories.

More RCTs evaluating interventions for treating constipation in pregnancy are needed. These should cover different settings and evaluate the effectiveness of various interventions (including fibre, osmotic, and stimulant laxatives) on improvement in constipation, pain on defecation, frequency of stools and consistency of stools.

PLAIN LANGUAGE SUMMARY

Interventions for treating constipation in pregnancy

What is the issue?

The term 'constipation' is defined as difficulty in passing stool and reduced frequency of bowel movements. It is characterised by discomfort, excessive straining, hard or lumpy stools, a sensation of incomplete evacuation, and infrequent bowel movements. Constipation is a common symptom experienced during pregnancy. This can result from a combination of factors, including changes in hormones during pregnancy affecting the digestive system, reduced physical activity and changes in dietary habits during pregnancy. In addition, as the baby grows it can press on the mother's intestines and cause digestive delays/obstructions.

Why is this important?

Constipation during pregnancy is associated with impaired quality of life and distress for pregnant women as well as physical problems including, occasionally, haemorrhoids. There are a range of suggested treatments with drugs, supplements or dietary modifications.

Generally, non-pharmacological interventions (changes in diet, water intake and exercise) are recommended initially, followed by pharmacological interventions if the non-pharmacological interventions fail or are insufficient. Pharmacological interventions include medications from a wide range of drug classes including lubricants, bulk-forming agents, osmotic laxatives, stimulant laxatives, stool softeners, and enemas and suppositories.

This review looked at the benefits of drug and non-drug interventions for constipation in pregnancy and whether they are safe for women and babies.

What evidence did we find?

We identified four studies, but only two studies (with a total of 180 women) provided data for analysis. The studies looked at stimulant laxatives compared with bulk-forming laxatives and dietary fibre supplementation versus no intervention. The included studies were judged to be of moderate quality.

We looked at two main comparisons. In the first, we found that stimulant laxatives may be more effective in improving constipation than bulk-forming laxatives (*moderate quality evidence*) but may also cause more abdominal discomfort (*low quality evidence*) and diarrhoea (*moderate quality evidence*) and we found no difference in women's satisfaction (*moderate quality evidence*). However, when we removed data relating to an intervention called [Normax](#) (dioctyl sodium sulphosuccinate and dihydroxy anthraquinone), which is no longer routinely used in pregnancy, there was no longer a clear difference between stimulant and bulk-forming laxatives in terms of abdominal discomfort and diarrhoea.

The second comparison, between fibre supplementation and no intervention, found that fibre supplementation may be effective in increasing the frequency of stools (*moderate quality evidence*). Fibre supplementation was associated with improved stool consistency as defined by trialists (hard stool decreased by 11% to 14%, normal stool increased by 5% to 10%, and loose stool increased by 0% to 6%).

There were no studies that looked at others types of interventions like osmotic laxatives, stool softeners, lubricant laxatives and enemas and suppositories.

What does this mean?

What little evidence there is, suggests that dietary fibre supplementation may increase the frequency of stools. If choosing between stimulant and bulk-forming laxatives, then stimulant may relieve constipation better but may cause more abdominal discomfort and diarrhoea.

More research in this area is needed.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Stimulant laxatives versus bulk-forming laxatives for treating constipation in pregnancy						
Patient or population: women with treating constipation in pregnancy Settings: trial located in UK Intervention: stimulant laxatives versus bulk-forming laxatives						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Stimulant laxatives versus bulk-forming laxatives				
Primary outcome - constipation improvement	486 per 1000	772 per 1000 (588 to 1000)	RR 1.59 (1.21 to 2.09)	140 (1 study)	⊕⊕⊕○ moderate ¹	
Primary outcome - pain on defecation - not reported	See comment	See comment	Not estimable	-	See comment	
Primary outcome - frequency of stools	Study population		Not estimable	0 (0 ²)	See comment	
	See comment	See comment				
	Moderate					
Primary outcome - consistency of stools	See comment	See comment	Not estimable	0 (0 ²)	See comment	
Secondary outcome - abdominal discomfort	Study population		RR 2.33 (1.15 to 4.73)	140 (1 study)	⊕⊕⊕○ moderate ¹	

	129 per 1000	300 per 1000 (148 to 608)			
	Moderate				
	129 per 1000	301 per 1000 (148 to 610)			
Secondary outcome - diarrhoea	Study population		RR 4.5 (1.01 to 20.09)	140 (1 study)	⊕⊕○○ low ^{1,3}
	29 per 1000	129 per 1000 (29 to 574)			
	Moderate				
	29 per 1000	131 per 1000 (29 to 583)			
Secondary outcome - women's satisfaction	Study population		RR 1.06 (0.77 to 1.46)	140 (1 study)	⊕⊕⊕○ moderate ¹
	500 per 1000	530 per 1000 (385 to 730)			
	Moderate				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Unclear risk of selection and assessment biases and high risk of performance bias

- ² No included study for this outcome
- ³ Wide range of confidence interval

BACKGROUND

Description of the condition

The term 'constipation' is defined as difficulty in passing stool and reduced frequency of bowel movements that is not secondary to an underlying cause (Moriarty 1992). It is characterised by discomfort, excessive straining, hard or lumpy stools, a sensation of incomplete evacuation, and infrequent defecation (Bradley 2007). Constipation is a common symptom experienced during pregnancy. This is the result of a combination of factors, including the effect of altered hormone levels on the gastrointestinal (GI) tract, mechanical effects of the growing fetus, reduced physical activity and changes in dietary habits (Cullen 2007). Gastrointestinal transit time is significantly prolonged in the second and third trimester (from 125 to 137 minutes) when compared with either the first trimester of pregnancy or the postpartum period (from 75 to 99 minutes) (Lawson 1985). In relation to hormones, an increase of progesterone reduces smooth muscle contractility, prolonging bowel transit time (Prather 2004). In addition, the compressive effects of the enlarging gravid uterus result in mechanical obstruction of the intestines. Other causes include decreased maternal activity, anxiety, iron supplementation and poor fluid intake. Commonly, many of these factors combine over the course of the pregnancy. Moreover, many women who are affected by constipation pre-conception tend to have worsening symptoms during pregnancy (Wald 2003). The prevalence of constipation in pregnancy ranges from 11% to 44% (Prather 2004; Bradley 2007; Shafe 2011; Trottier 2012). Part of this significant variation is due to variation in the definitions of constipation (Shafe 2011).

Constipation may be complicated by haemorrhoids due to the excessive straining associated with the condition (Longo 2010). Constipation is connected with reduced quality of life for various reasons including discomfort and negative body image perception, and may have broader psychological complications including frustration and low mood (Irvine 2002; Portalatin 2012; Johnson 2014). Those suffering constipation are more likely to report poor general health, poor physical functioning, reduced vitality and poorer social functioning (Wald 2007). The Rome II Criteria is a standard clinical measure of assessing functional constipation; however diagnosis is complex, requiring relatively detailed recall of the patient's bowel movements (Drossman 2006). Cullen proposed a simplified diagnostic criterion based on a history of low frequency of stools (less than three stools per week), hard stools and/or difficulties with evacuation of faeces (Cullen 2007). This self-reported criterion was found to be more sensitive than the Rome II criterion and has the advantage of being more practical for both healthcare worker and patient (Ponce 2008).

Description of the intervention

In this review, we will consider pharmacological and non-pharmacological interventions for treating constipation in pregnancy. Generally, non-pharmacological interventions are recommended initially, followed by pharmacological interventions if the non-pharmacological interventions fail or are insufficient; however there is no formal guideline on how to approach this (NICE 2008). The British National Formulary suggests if laxatives are required in pregnancy to consider starting with a bulking agent, then an osmotic agent and then a stimulant; however this is not a formal guideline (BNF 2010). A 2009 survey of 1648 pregnant women with constipation found that 44.2% had been treated with laxatives, a figure which had increased since an earlier survey in 2005 (Shafe 2011). Pharmacological interventions include medications from a wide range of drug classes including lubricants, bulk-forming agents, osmotic laxatives, stimulant laxatives, stool softeners, and enemas and suppositories (Portalatin 2012). Non-pharmacological interventions include changes in diet, water intake and exercise. In this review, we categorise medicinal fibres, such as psyllium, and synthetic polymers, such as polycarbophil and methylcellulose, into pharmacological interventions; dietary fibres are classified under non-pharmacological interventions.

A report from the US recommends the amount of dietary fibre to be 20 to 35 g/day (Marlett 2002). The suggested oral dose of bulk-forming laxatives is: 6.4 to 10 g/day (psyllium), 4.8 to 9.6 g/day (methylcellulose), 2 to 8 g/day (polycarbophil); of osmotic laxatives is 15 to 30 mL/day (lactulose), 15 to 30 mL/day (sorbitol), 17 to 34 mL/day (polyethylene glycol (PEG)), 30 to 45 mL/day (magnesium oxide); and of stimulant laxatives is: 7.5 to 30 mg/day (senna), 10 to 15 mg/day orally or 10 mg/day rectally (bisacodyl) (Prather 2004). The suggested dose of glycerol suppository is 2250 mg (MIMS 2014). For docusate sodium it is 50 to 500 mg/day orally in one to four divided doses or 0.12 g rectally as docusate sodium in a 10 g enema gel (MIMS 2014).

Pharmacological interventions

Laxatives, as with any medication in pregnancy, should ideally be effective, non-teratogenic, not excreted in breast milk and well-tolerated.

The LUCK (Laxative Usage in patients with GP-diagnosed Constipation in the UK) study was a cohort study using the General Practice Research Database (GPRD). The highest prevalence was observed amongst females aged between 30 and 44, possibly reflecting an increase in the risk of constipation during pregnancy. The prescribing trends of laxatives in pregnancy over the five-year study period have been changing from lactulose to macrogol.

Lubricant laxatives

Lubricant laxatives, such as mineral oil or paraffin, have no direct pharmacological effect on the gastrointestinal mucosa but instead have a direct lubricating effect on stool (Shafe 2011). They are not commonly prescribed in pregnancy according to the LUCK study (

Shafe 2011). An important potential complication associated with long-term use is maternal malabsorption of fat-soluble vitamins (e.g. vitamins A, D, E and K) (Cullen 2007). In the case of vitamin K, this can lead to hypoprothrombinaemia and haemorrhage (Cullen 2007).

Bulk laxatives

Bulk laxatives such as psyllium, methylcellulose and calcium polycarbophil are fibre supplements which expand with water to increase stool bulk (Leung 2011). They are generally safe for long-term use in pregnant women and are often the first line of treatment for constipation in pregnancy that does not respond to non-pharmacological interventions (Trottier 2012). Bulk laxatives are generally understood to be well-tolerated, however, a report by Tytgat indicates that they may cause abdominal bloating and cramping at therapeutic doses (Tytgat 2003).

Osmotic laxatives

Osmotic laxatives are a group of hyperosmolar laxatives characterised by very low levels of absorption, which increase stool water content due to their osmotic properties (Trottier 2012). They include subcategories such as salts, saccharine, alcohols and macrogols (Klaschik 2003). In the LUCK study, they were the most commonly prescribed type of laxative to pregnant women with constipation (Shafe 2011). There are a number of established side-effects: first, saccharated osmotics (e.g. lactulose or sorbitol) may cause flatulence and bloating (Portalatin 2012) and, in women with nausea, they may exacerbate it (Wald 2003). Second, salt osmotics (e.g. magnesium or sodium salts) may cause maternal sodium retention (Cullen 2007). Finally, polyethylene glycol (PEG) or macrogol may cause abdominal bloating and cramps (Portalatin 2012).

Stimulant laxatives

Stimulant laxatives, such as senna and bisacodyl, stimulate peristalsis. They are relatively infrequently used in pregnancy in the LUCK study (Shafe 2011). Stimulant laxatives may be accompanied by side-effects such as abdominal cramps, salt overload, hypokalaemia, hyponatraemia, and dehydration from severe diarrhoea (Wald 2003; Portalatin 2012). There is a range of specific side-effects: senna, an anthroquinone, may cause abdominal cramps (Trottier 2012) and also small amounts are excreted in breast milk (Cullen 2007), however is not associated with teratogenic effects and is considered to be safe in pregnancy (Acs 2002; MIMS 2014). Diphenylmethanes (e.g. bisacodyl) may cause abdominal discomfort, diarrhoea and hypokalaemia (MIMS 2014), and castor oil may cause premature uterine contractions (Cullen 2007).

Stool softeners

Stool softeners, also known as emollient laxatives, belong to a group of anionic surfactants that allow water to enter the stool more readily (Trottier 2012). The most frequently used are the docusate salts, sodium docusate and calcium docusate, although there are other forms also available (Trottier 2012). They are generally considered to have no significant adverse effects based on the results of several studies (Trottier 2012). However, one study did show that docusate sodium may be associated with symptomatic hypomagnesaemia in the neonate (Wald 2003).

Enemas and suppositories

Enemas and suppositories are preparations of the previously discussed classes of laxatives which are administered rectally (Klaschik 2003). They are generally considered for short-term relief after oral laxatives have failed (Clemens 2013). The key advantages are that they are locally acting and can give rapid relief (Clemens 2013). There are certain issues including inconvenient mode of administration, local irritation, and discomfort (Twycross 2012; MIMS 2014).

Non-pharmacological interventions

The key non-pharmacological interventions are increasing dietary fibre intake, increasing water intake and increasing light physical activity (Prather 2004). These interventions provide a starting point for the management of constipation in pregnancy. They are generally understood to have few side-effects; however, high-fibre diets may cause abdominal bloating or flatulence (Tytgat 2003).

How the intervention might work

Pharmacological interventions

Lubricant laxatives

Lubricant laxatives act as a lubricant to coat the stool, and also soften the stool, both of which mean that passing the stool is easier (Klaschik 2003). They are relatively pharmacologically inert, that is, the effect is a direct one (Klaschik 2003).

Bulk laxatives

Bulk laxatives increase fecal water content, stimulate bowel motility, and decreased colonic transit time. Their desired effects may take a few days to achieve, so it is not appropriate for acute treatment (Tytgat 2003). The dose of bulk laxatives can be titrated to achieve continued relief throughout pregnancy as predisposition to constipation changes (Longo 2010). These agents are

purported to be the most physiologic and safest pharmacological therapy for constipation in pregnancy (Wald 2003). Psyllium (*Ispaghula*) has high water-binding capacity and is known to ferment in the colon. Side-effects include delayed gastric emptying, loss of appetite, and, less frequently, serious acute allergic reactions and asthma (Vaswani 1996; Xing 2001). Methylcellulose, a synthetic polymer fibre, leads to resistance to bacterial fermentation. It absorbs water into the colonic lumen thereby increasing fecal mass, stimulating motility and reducing colonic transit time. Polycabophil, a hydrophilic resin, is not metabolised by intestinal bacteria, therefore may be less likely to cause gas and bloating. Where women are unresponsive to bulking agents alone, combination therapy with other agents should be considered (Portalatin 2012).

Osmotic laxatives

Osmotic laxatives are poorly absorbed by the intestine thus increase fluid retained in the bowel by increasing intra-luminal osmotic pressure (Prather 2004). As mentioned, the different types include salts, saccharine, alcohols and macrogols (Klaschik 2003). Saline osmotics (e.g. magnesium and sodium salts) are inadvisable for pregnant women because they can cause maternal sodium retention (Wald 2003). Saccharated osmotic (e.g. lactulose and sorbitol) promote intestinal motility and stool frequency. Lactulose is a poorly absorbed synthetic disaccharide metabolised by colonic bacteria. Macrogol, also known as Polyethylene glycol (PEG), is conventionally an osmotic laxative, however it may be prepared with other laxatives to form an isosmotic laxative (Corazziari 2000). It modifies stool consistency and increases stool bulk without significant fluid shifts, hence theoretically has less risk of dehydration or severe diarrhoea (Corazziari 2000; Grossmann 2000).

Stimulant laxatives

Where constipation is unresponsive to bulk or osmotic laxatives, stimulant laxatives may be considered (Prather 2004). They have a fast onset of action, working within hours in a dose-dependent manner (Portalatin 2012). Low doses prevent absorption of water and sodium, however high doses stimulate secretion of sodium into the colonic lumen causing an osmotic fluid shift, which may result in abdominal cramping and severe diarrhoea (Portalatin 2012). Anthraquinones (e.g. senna) increase electrolyte transportation into the colonic lumen and stimulate myenteric plexuses to increase intestinal motility. They induce defecation six to eight hours after ingestion (Portalatin 2012). Diphenylmethanes (e.g. bisacodyl) affect the colon in the same way as anthraquinones. These laxatives are most suitable for single-dose use in pregnant women with temporary constipation (Portalatin 2012).

Stool softeners

Stool softeners facilitate the passage of water into the stool mass by lowering its surface tension (Trottier 2012). Docusate sodium, and other docusate salts, soften stool by facilitating intestinal fluid secretion into the fecal mass (Portalatin 2012). Mineral oil, another example, is an indigestible liquid compound which softens fecal contents by reducing water absorption and by direct lubrication (Portalatin 2012).

Enemas and suppositories

Enemas are solutions that take various forms including water, phosphate and sugar. Phosphate enemas are hypertonic solutions, which increase stool water content due to their osmotic properties and also stimulate the rectal mucosa (Portalatin 2012). Saline enemas also have osmotic properties and may cause rectal distension and discomfort (Portalatin 2012). Docusate sodium enemas act as a lubricant type of laxative and also increase the penetration of fluid into the faeces (MIMS 2014).

Enemas and suppositories (glycerine, bisacodyl, phosphate) act by local direct contact with the rectal mucosa after dissolution of the suppositories. Their effect on reducing constipation is rapid (Clemens 2013). As they are simply rectally-administered preparations of the previously discussed oral laxatives, their mechanism of action is similar, albeit local (Klaschik 2003). Suppositories contain an active laxative compound dispersed in a base ingredient such as vegetable oil or water. Bisacodyl suppositories are available in two preparations including polyethylene glycol-based and hydrogenated vegetable oil-based (Potter 2005). Bisacodyl, a diphenylmethane derivative, has stimulant properties and acts on neurons mainly in the large intestine, stimulating motility (Portalatin 2012). The onset of action of bisacodyl suppository is 20 minutes to three hours (mean one hour) (Twycross 2012), so they are useful for relieving constipation quickly. In addition, they can be helpful for pregnant women who cannot swallow tablets. Where possible, wearing clean gloves to insert the suppository maintains personal hygiene. Glycerin is an osmotic dehydrating agent that works by stimulating the lining of the intestine, as well as increasing fecal water content, making it easier for stools to pass (Kyle 2006; Portalatin 2012).

Non-pharmacological interventions

There are various non-pharmacological interventions. The National Institute for Health and Care Excellence (NICE) clinical guidelines on routine antenatal care recommend a change in diet to increase dietary fibre for treating constipation in pregnancy (Vazquez 2010). Naturally-occurring dietary fibre comes from plants and a high-fibre diet can include things like fruit, vegetables and wholegrain cereals (Muller-Lissner 1988). Dietary fibre is indigestible and retains water, thus increasing fecal weight and volume (Muller-Lissner 1988). Ensuring adequate water intake is thought to be an important cofactor to dietary change, however

the evidence is unclear on this intervention (Vazquez 2010). Moderate physical exercise, defined as any activity that is equivalent in difficulty to brisk walking, promotes regular bowel movements in pregnancy (Pate 1995; Derbyshire 2006). The recommendation for pregnant women with no medical or obstetric complication is 30 minutes a day of moderate exercise on most, if not all, days of the week (Artal 2003).

Why it is important to do this review

Constipation is a very common symptom during pregnancy, and is associated with impaired quality of life, haemorrhoids, and distress for pregnant women. Many interventions are available and have varying side-effect profiles. Pharmacological interventions may be considered when diet and lifestyle modifications are not effective. An understanding of the potential teratogenicity and safety of medications used in pregnancy is vital for the clinician managing these pregnant women. This review is important for establishing the safety and efficacy of different treatments for constipation in pregnancy. The previous Cochrane review on this topic (Jewell 2001) is now out of date and has been relinquished by the authors.

OBJECTIVES

To assess the effectiveness and safety of interventions (pharmacological and non-pharmacological) for treating constipation in pregnancy.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (including trials using a cluster-randomised design and quasi-randomised trials) evaluating interventions for constipation in pregnancy. Studies using a cross-over design, or studies reported only in abstract form (without full text) were not eligible for inclusion.

Types of participants

Pregnant women complaining of constipation, defined as infrequent and difficult defecation.

Types of interventions

All interventions (pharmacological and non-pharmacological agents) for treating constipation in pregnancy were considered. We compared one intervention (pharmacological or non-pharmacological) against another intervention, placebo or no treatment. We did not pool all the pharmacological or non-pharmacological interventions together.

Types of outcome measures

Primary outcomes

1. Improvement in constipation (as measured/ defined by trialists) (outcome not prespecified in our published protocol - Rungsiprakarn 2014)
2. Pain on defecation
3. Frequency of stools
4. Consistency of stools (as measured/defined by trialists)

During the review process, we found that studies reported changes in symptoms in different ways. To capture all data available, we added “improvement in constipation”. This broader banner encapsulates a more woman-centred understanding of constipation in pregnancy.

Secondary outcomes

Maternal

1. Women's satisfaction
2. Quality of life
3. Abdominal discomfort (cramping, bloating, and flatulence)
4. Dehydration
5. Diarrhoea
6. Electrolyte imbalance
7. Acute allergic reactions
8. Asthma

Neonatal/fetal

1. Electrolyte imbalance

Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We contacted the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register (30 April 2015).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (OVID);
3. weekly searches of Embase (OVID);
4. monthly searches of CINAHL (Ebsco);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE, Embase and CINAHL, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

In addition, we searched [ClinicalTrials.gov](#) and the WHO International Clinical Trials Registry Platform (ICTRP) (30 April 2015) for unpublished, planned and ongoing trial reports, using the terms listed in [Appendix 1](#).

Searching other resources

We searched the reference lists of retrieved studies.

We did not apply any language or date restrictions.

Data collection and analysis

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Selection of studies

Two review authors, Phassawan Rungsiprakarn (PR) and Pisake Lumbiganon (PL) independently assessed for inclusion all of the potentially relevant studies we identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted a third review author, Malinee Laopaiboon (ML). We created a study flow diagram to map out the number of records identified, included and excluded.

Data extraction and management

We designed a form to extract data. For eligible studies, PR, Ussanee Sangkomkamhang (US) and ML extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted PL. We entered data into Review Manager software ([RevMan 2014](#)) and checked the data for accuracy. When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors, PR and ML, independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We resolved any disagreement by discussion or by consulting PL.

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the method as:

- low risk of bias (e.g. telephone or central randomisation; consecutively-numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes. We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we re-included missing data in the analyses which we undertook.

We assessed the methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we had about other possible sources of bias.

We assessed whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - see *Sensitivity analysis*.

The quality of the evidence was assessed using the GRADE approach (Schunemann 2009) in order to assess the quality of the body of evidence relating to the following outcomes for the main comparisons:

1. improvement in constipation;
2. frequency of stools;
3. abdominal discomfort;
4. diarrhoea;
5. women's satisfaction.

We used GRADEprofiler (GRADE 2014) to import data from Review Manager 5.3 (RevMan 2014) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes were produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

For dichotomous data we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we used the mean difference if outcomes were measured using the same scale between trials. We planned to use

the standardised mean difference to combine trials that measured the same outcome with different scales.

Unit of analysis issues

Cluster-randomised trials

In future updates of the review, we will include cluster-randomised trials in the analyses along with individually-randomised trials. We will adjust their standard errors using the methods described in the *Handbook* using an estimate of the intracluster correlation coefficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a subgroup analysis to investigate the effects of the randomisation unit.

Cross-over trials

Cross-over trials were not eligible for inclusion in this review.

Multi-armed trials

We included one multi-armed trial in the analyses. We included the relevant intervention groups in a pair-wise comparison of intervention groups that met the criteria for including studies in the review. We combined groups to create a single pair-wise comparison using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

For included studies, we noted levels of attrition. We explored the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. In future updates of the review for all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

In future updates of the review, we will assess statistical heterogeneity in each meta-analysis using the T^2 , I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if an I^2 is greater than 30% and either a T^2 is greater than zero, or there is a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

In future updates of the review, if there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014). In future updates of the review we will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

If we use random-effects analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of T^2 and I^2 .

Subgroup analysis and investigation of heterogeneity

Planned subgroup analyses were not conducted due to insufficient data. In future updates of this review, if we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

We plan to carry out the following subgroup analyses.

1. Type of pharmacological agents; bulk-forming laxatives, stool softeners, osmotic laxatives, and stimulant laxatives.
2. Short-term (two weeks or less) intervention use versus prolonged (more than two weeks) use of the intervention.
3. Different route of interventions such as oral route versus rectal route.

The following outcomes will be used in subgroup analysis: increased frequency of defecation and softened stools. We will assess subgroup differences by the interaction tests available within RevMan ([RevMan 2014](#)). We will report the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We did not carry out our planned sensitivity due to insufficient data. In future updates, if required, we will carry out sensitivity analyses for all primary outcomes to explore the effect of trial quality based on concealment of allocation. We will exclude trials rated as 'high risk of bias' or 'unclear risk of bias' for allocation concealment in order to assess any substantive difference in the overall result.

In our comparison of stimulant laxatives versus bulk-forming laxatives (comparison 1) we included data from a trial with four treatment arms (two stimulant laxatives [Senokot and Normax] and

two different bulk-forming laxatives). However, one of the stimulant laxatives, Normax (dioctyl sodium sulphosuccinate and dihydroxy anthraquinone) is no longer used for the treatment of constipation in pregnant women (and package information advises that it should not be used during pregnancy or breastfeeding). We therefore carried out a sensitivity analysis (not prespecified in our protocol) with the data for Senokot and Normax presented separately.

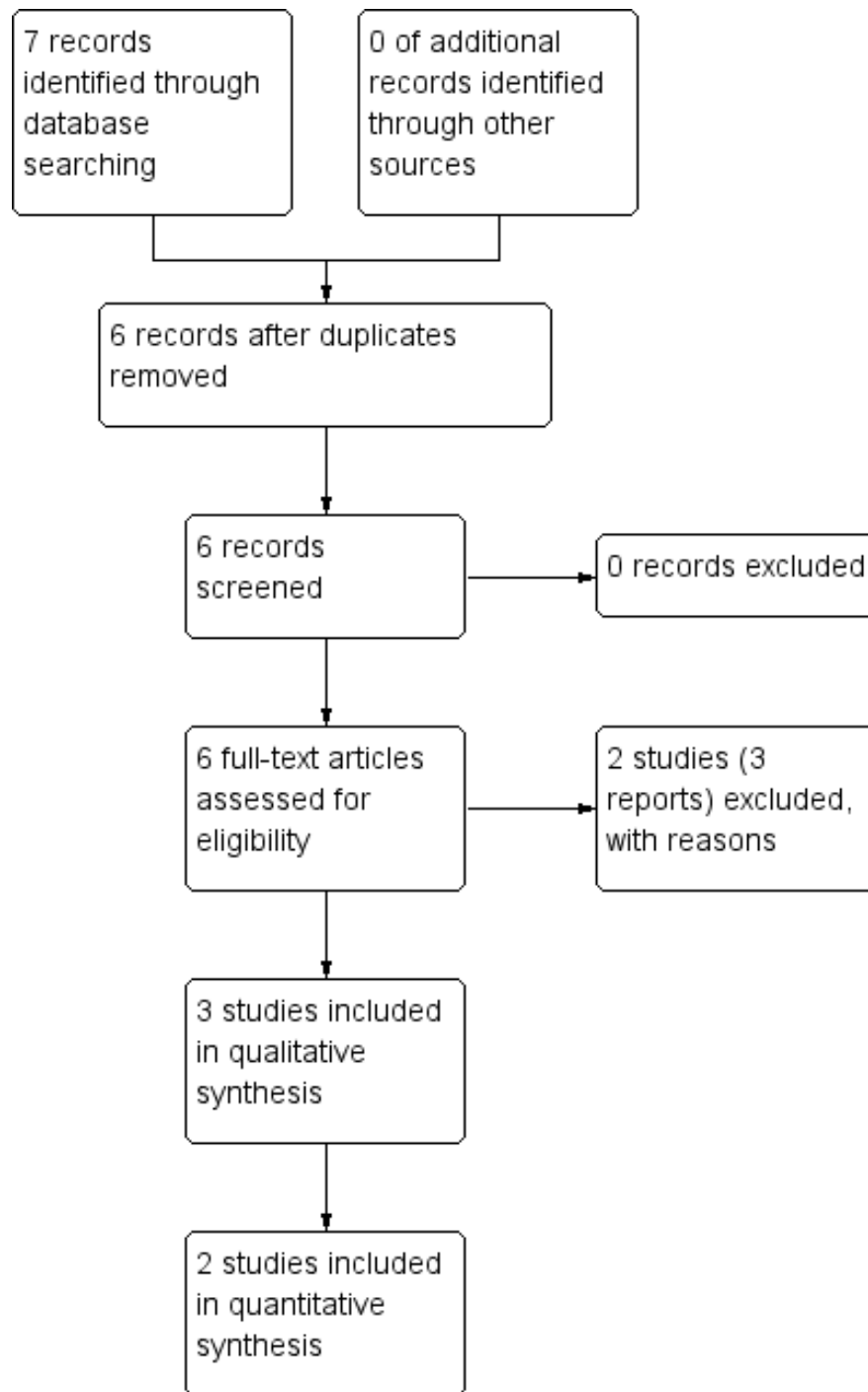
RESULTS

Description of studies

Results of the search

See: [Figure 1](#).

Figure 1. Study flow diagram.



The search identified seven trial reports (relating to six studies) published between 1957 and 2013. Two reports were from the same study ([Ghahramani 2013](#)). Four studies were included in this review ([Greenhalf 1973](#); [Gregersen 1985](#); [Anderson 1985](#); [Amadeo 1990](#)) and two were excluded ([Browne 1957](#); [Ghahramani 2013](#)).

Included studies

For detailed characteristics of the included studies, see [Characteristics of included studies](#). [Amadeo 1990](#) (40 pregnant women) did not report any data relevant to the primary or secondary outcomes of this review. [Gregersen 1985](#) (250 pregnant women) also did not contribute any usable data to the review.

Design

All the included studies were reported to be randomised controlled trials (RCTs) ([Greenhalf 1973](#); [Gregersen 1985](#); [Anderson 1985](#); [Amadeo 1990](#)). It was not clear whether they were RCTs or quasi-RCTs because the sequence generation was unclear.

Sample size

The total number of participants included in trials contributing data to the review was 180 pregnant women. There was no loss to follow-up. The sample size of each study varied from 40 to 140.

Setting

Two trials were conducted in the UK ([Greenhalf 1973](#); [Anderson 1985](#)) whilst the third, [Amadeo 1990](#), was conducted in Italy. [Gregersen 1985](#) took place in Denmark.

Participants

[Anderson 1985](#) studied 20 to 38 year old women in their third trimester who had no medical problems aside from constipation. [Amadeo 1990](#) studied 19 to 42 year old pregnant women with primary constipation. [Greenhalf 1973](#) included both constipated pregnant and puerperal breast-feeding women with constipation; however, only data from pregnant women were used in this review. [Gregersen 1985](#) studied pregnant women with constipation (20 to 36 weeks' gestation).

Interventions

[Greenhalf 1973](#) (n = 140) compared two types of stimulant and two types of bulk-forming laxatives: Senokot, two tablets daily, consisting of 7 mg of standard senna; Normax, two capsules a day, contains 60 mg of dioctyl sodium sulphosuccinate and 50 mg of

dihydroxyanthraquinone; Normacol standard, two teaspoonfuls a day, contains sterulia British Pharmaceutical Codex (B.P.C.) and frangula B.P.C.; Normacol special, two teaspoonfuls a day, contains sterulia B.P.C.. Each intervention had 35 participants. [Gregersen 1985](#) (n = 250) compared fibre tablets (Dumovital) with placebo tablets. Women in the intervention arm received Dumovital fibre tablets (n = 133) - two initial weeks with no tablets, third week, three per day, fourth week, six per day, weeks five to nine, nine tablets per day. Women in the placebo arm received placebo tablets (n = 117) according to an identical regimen. [Anderson 1985](#) (n = 40) compared two different dietary fibre supplements and no intervention. After two weeks of baseline observation, the women were randomly allocated into one of three groups (Fibermed, a 10 g corn-based biscuit (n = 13); 23 g wheat bran (n = 14) or no intervention (n = 13)) for a further two weeks. [Amadeo 1990](#) (n = 40) compared glucomannan and minerals (n = 20) with placebo (n = 20). Women in the intervention group received Dimanel 500 mg to 1500 mg (500 mg/capsule). If symptoms persisted, the dose was raised to 1000 mg twice daily. Women in the control group received a placebo (formulation unspecified) two to three capsules twice daily which could be raised by two capsules twice daily keeping in line with the treatment group.

Outcomes

[Greenhalf 1973](#) (n = 140) had improvement in constipation as the primary outcome and reported secondary outcomes of maternal abdominal discomfort and diarrhoea. [Anderson 1985](#) (n = 40) had frequency of stools and a change to a softer stool consistency as the primary outcomes. Thus three primary outcomes (improvement in constipation, frequency of stools and consistency of stools) and three secondary outcomes (abdominal discomfort, diarrhoea and women's satisfaction) were reported in these two included studies. One study (n = 40) did not have data on relevant outcomes data ([Amadeo 1990](#)).

[Gregersen 1985](#) measured the number of bowel movements in a 14-day period, but the data were not presented in usable form. [Gregersen 1985](#) also reported reasons why 110/240 women failed to complete the study, and these reasons included our secondary outcome of diarrhoea. However, the adverse effects outcomes were only reported for women leaving the study, and so we did not consider the data complete or usable.

Excluded studies

For detailed characteristics of the excluded trials, see [Characteristics of excluded studies](#). We excluded [Browne 1957](#) because the participants were not restricted to pregnant women. We excluded [Ghahramani 2013](#) be-

cause the study was investigating prevention of constipation, not treatment.

Risk of bias in included studies

Risk of bias in the included studies varied. For sequence generation, allocation concealment, and blinding, the two included studies that contributed data had unclear or high risk of bias. However, for incomplete outcome data, selective reporting, and other biases, the risk of bias was low.

We classified the overall risk of bias of three studies ([Amadeo 1990](#); [Anderson 1985](#); [Greenhalf 1973](#)) as moderate and one study ([Gregersen 1985](#)) as high.

For an overview of review authors' judgments about each 'Risk of bias' item for individual included studies, see [Figure 2](#) and [Figure 3](#).

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

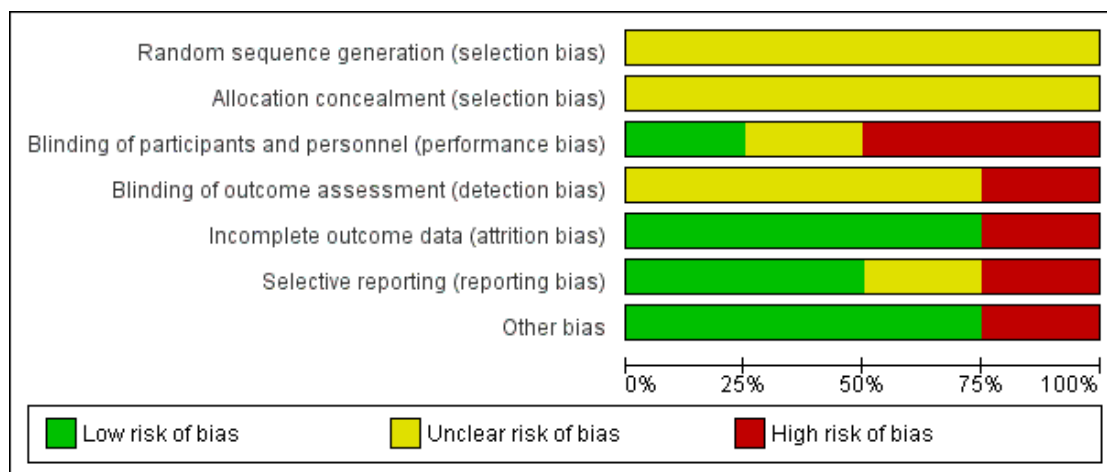


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Amadeo 1990	?	?	?	?	+	?	+
Anderson 1985	?	?	-	-	+	+	+
Greenhalf 1973	?	?	-	?	+	+	+
Gregersen 1985	?	?	+	?	-	-	-

Allocation

Three studies (Greenhalf 1973; Gregersen 1985; Amadeo 1990) did not report details of sequence generation or allocation concealment. One study was not clear on the sequence generation and allocation concealment (Anderson 1985). We therefore classified all studies as having an unclear risk of selection bias.

Blinding

One study (Amadeo 1990) did not provide adequate information about blinding. We judged this study as unclear risk of detection and performance bias.

Two studies (Greenhalf 1973; Anderson 1985) did not use an identical placebo and were judged as high risk of performance bias. For detection bias, one study (Greenhalf 1973) did not provide any information and was judged as unclear risk. However, the outcome assessors in one study (Anderson 1985) were not blinded, we therefore judged this study to be as high risk for detection bias. Gregersen 1985 was described as placebo-controlled and double-blind. We were unclear if women and staff would have been aware of assignment, but blinding may have been achieved because women self-administered tablets in the community. We assessed the trial as of low risk for performance bias. Women self-reported outcome data, and we assessed the trial as of unclear risk for detection bias.

Incomplete outcome data

All recruited participants were in the analyses of all three studies (Greenhalf 1973; Anderson 1985; Amadeo 1990); we therefore judged them to be at low risk of attrition bias.

Gregersen 1985 was at high risk of attrition bias because 110/240 women failed to complete the study, some due to adverse effects of treatment. These side-effects data are not fully reported and not usable.

Selective reporting

All reported outcomes were pre-specified in the method part of all three studies (Greenhalf 1973; Anderson 1985; Amadeo 1990). We therefore judged them to be at a low risk of selective reporting bias. Gregersen 1985 reported side-effects for only the women who left the study and was assessed as of high risk of bias.

Other potential sources of bias

None identified, apart from Gregersen 1985, a trial we considered to be of high risk because the primary outcome was reported in graph form only, rendering the data unusable.

Effects of interventions

See: [Summary of findings for the main comparison Stimulant laxatives versus bulk-forming laxatives for treating constipation in pregnancy](#); [Summary of findings 2 Fibre supplementation versus no intervention for treating constipation in pregnancy](#)

During the review process we found that studies report changes in symptoms in different ways. To capture all data available, it was essential that the primary outcomes were altered. One study (Amadeo 1990) did not contribute to any comparison because there were no relevant data on the translated document. Gregersen 1985 also contributed no usable data.

Comparison 1 - Stimulant laxatives versus bulk-forming laxatives

Primary outcomes

One study (Greenhalf 1973), involving 140 women, provided data for this comparison.

No data were identified for any of this review's prespecified primary outcomes: pain on defecation, frequency of stools and consistency of stools.

Improvement in constipation, was higher in those women taking stimulant laxative compared with bulk-forming laxatives (risk ratio (RR) 1.59, 95% confidence interval (CI) 1.21 to 2.09; 140 women, one study ([Analysis 1.1](#))).

Secondary outcomes

Data were available for three secondary outcomes: **abdominal discomfort**, **diarrhoea** and **women's satisfaction**. Pregnant women who received stimulant laxatives had more **abdominal discomfort** (RR 2.33, 95% CI 1.15 to 4.73; 140 women, one study, ([Analysis 1.2](#))), borderline difference in **diarrhoea** (RR 4.50, 95% CI 1.01 to 20.09; 140 women, one study ([Analysis 1.3](#))) than those who were given bulk-forming laxatives and no difference in **women's satisfaction** (RR 1.06, 95% CI 0.77 to 1.46; 140 women, one study ([Analysis 1.4](#))). For this review's other secondary outcomes, there were no data available for **quality of life**, **dehydration**, **electrolyte imbalances**, **acute allergic reaction** or **asthma**.

Comparison 2 - Stimulant laxatives versus bulk-forming laxatives (Sensitivity analysis, Senokot and Normax data separated)

In comparison one we combined the data for two different stimulant laxatives (Senokot and Normax) and compared them

with combined data for two similar bulk-forming laxatives (Normacol standard and Normacol special). One of the stimulant drugs, Normax (dioctyl sodium sulphosuccinate and dihydroxy anthraquinone) is no longer used for the treatment of constipation in pregnant women (and the [package information](#) advises against its use during pregnancy or breastfeeding). We therefore carried out a non-prespecified sensitivity analysis with the data for Senokot and Normax presented separately. Results for Senokot and Normax were similar, and results for the individual drugs largely reflect findings for the combined analysis.

Compared with bulk-forming laxatives both Senokot and Normax led to an improvement in constipation (RR 1.53, 95% CI 1.03 to 2.26; participants = 70, and, RR 1.65, 95% CI 1.13 to 2.41; participants = 70, respectively). Comparison one (combined data) showed that stimulant drugs increased abdominal discomfort and diarrhoea compared with bulk-forming laxatives, but when data for Senokot and Normax were presented separately there was no clear difference between groups, although the direction and size of effect was similar for both drugs. There was no clear difference between groups in terms of women's satisfaction with different types of laxatives, with similar numbers of women (approximately half) rating Senokot, Normax and bulk-forming laxatives as good or acceptable ([Analysis 2.4](#)).

Comparison 3 - Fibre supplementation versus no

intervention

Primary outcomes

One study ([Anderson 1985](#)), involving 40 women, provided data for this comparison. [Geggersen 1985](#) was relevant to this comparison, but there were no usable data in the trial report.

No data were identified for one of this review's prespecified primary outcomes: **pain on defecation or improvement in constipation**. Data were available for **frequency of stools** and **consistency of stools**. Pregnant women who received fibre supplementation had higher frequency of stools than those in the no intervention group (mean difference (MD) 2.24 times per week, 95% CI 0.96 to 3.52; 40 women, one study ([Analysis 3.1](#))). Similarly, [Anderson 1985](#) reported that fibre supplementation was associated with improved stool consistency as defined by trialists (hard stool decreased by 11% to 14%, normal stool increased by 5% to 10%, and loose stool increased by 0% to 6%) (see [Table 1](#)). [Anderson 1985](#), reported these changes in stool consistency as being different for bran compared with no intervention but not so for Fibermed compared with placebo.

Secondary outcomes

There were no usable data available for **women's satisfaction, quality of life, abdominal discomfort, dehydration, diarrhoea, electrolyte imbalances, acute allergic reaction or asthma**.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Fibre supplementation versus no intervention for treating constipation in pregnancy						
Patient or population: Women being treated for constipation in pregnancy Settings: trial located in UK Intervention: Fibre supplementation versus no intervention						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Fibre supplementation versus no supplement				
Primary outcome - frequency of stools		The mean frequency of stools in the intervention groups was 2.24 higher (0.96 to 3.52 higher)		40 (1 study)	⊕⊕⊕○ moderate ¹	
Primary outcome - pain on defecation - not reported	See comment	See comment	Not estimable	-	See comment	
Primary outcome - improvement in constipation - not reported	See comment	See comment	Not estimable	-	See comment	
Primary outcome - consistency of stools - not reported	See comment	See comment	Not estimable	-	See comment	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval;						

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Unclear risk of selection and assessment biases and high risk of performance bias

DISCUSSION

Summary of main results

There was an overall paucity of data with only two of the four included studies contributing data to the review. The included studies were judged to be of moderate risk of bias. Only two comparisons with one study each were able to be analysed. No meta-analysis was possible.

The results suggest that stimulant laxatives were significantly more effective than bulk-forming laxatives in terms of improvement in constipation, but were associated with significantly higher abdominal discomfort and diarrhoea. We added a new primary outcome 'improvement in constipation' at the review stage. This review's prespecified primary outcomes: pain on defecation, frequency of stools and consistency of stools are components of constipation. It became obvious during the review process that studies report changes in symptoms in different ways, as such, to capture all data available, it was essential that the primary outcomes were altered. Furthermore, this broader banner encapsulates a more woman-centred understanding of constipation in pregnancy.

Fibre supplementation was more effective for treating constipation in pregnant women than no intervention in terms of frequency and consistency of stools. The results on consistency of stools were re-reported (not analysed in this review).

Overall completeness and applicability of evidence

There were only four included studies suggesting that there are very little randomised data available. Furthermore, there were no additional eligible studies since the previous Cochrane review on this topic in 2001 (Jewell 2001).

We feel that with the search strategy conducted this does indeed reflect the full gamut of randomised data available. Of the studies included, the two that provided data were both set in the UK whilst the others were set in Italy and Denmark. Confining the population studied to high-income countries introduces issues around generalisability.

No data were reported for the following primary outcomes: pain on defecation.

No usable data were identified for any of this review's secondary outcomes: quality of life; dehydration; electrolyte imbalance; acute allergic reaction; or asthma.

Furthermore, given the limited data available on adverse effects, it is difficult to infer the acceptability of the treatments studied.

Quality of the evidence

The two of four included studies that contributed data to this review had only 180 women. The overall risk of bias of these two

studies was moderate. The results should be interpreted with caution. All five available outcomes including improvement in constipation, frequency of stools, abdominal discomfort, diarrhoea and women's satisfaction were assessed with the GRADE software. These were assessed to be of moderate quality except for evidence on abdominal discomfort, which was assessed to be of low quality. The prespecified primary outcomes 'pain on defecation' and 'consistency of stools' were not able to be analysed due to lack of data. The scores of moderate and low quality reflect the assessment of bias, wide confidence intervals and lack of meta-analysis.

Potential biases in the review process

We followed methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to minimise biases in the review process.

Agreements and disagreements with other studies or reviews

We are not aware of any other systematic reviews assessing the effectiveness and adverse effects of interventions for constipation during pregnancy. In this review, no further studies were added since the previous Cochrane review on this topic was published by Jewell 2001, as such, there are no major changes to its conclusions. This review is in agreement with one of its key findings, that more randomised data are required in order to draw firm conclusions on the management of constipation in pregnancy.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to recommend the use of dietary fibre supplementation, stimulant and bulk-forming laxatives for treating constipation during pregnancy.

There were no data for the comparison among others types of interventions such as osmotic laxatives, stool softener, lubricant laxatives and enemas and suppositories.

Implications for research

More randomised controlled trials covering different settings (high-, middle-, and low-income countries) evaluating the effectiveness of various interventions such as dietary fibre, osmotic, and stimulant laxatives on improvement in constipation, pain on defecation, frequency of stool and consistency of stools are needed.

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The named authors alone are responsible for the views expressed in this publication.

As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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- * Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Amadeo 1990

Methods	Randomised controlled trial.
Participants	19-42 year old pregnant women presenting with primary constipation
Interventions	A formulation of glucomannan and minerals (Dimanel noctre) (n = 20) and placebo (no mention of what the substance was) (n = 20). The dose of Dimanel was 500-1500 mg (500 mg/capsule). If symptoms persisted the dose was raised to 1000 mg twice daily
Outcomes	Relief of constipation (palpable faecal mass, abdominal pain, painful bowel evacuation and abdominal or/and rectal fullness feeling)
Notes	This study was set in Italy. This trial did not contribute data as the results of the primary outcomes were not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information available.
Allocation concealment (selection bias)	Unclear risk	Quote (from translation): "Paper stated the trial was randomised and double blinded. Nevertheless, it only states that participants were divided into 2 equal groups. There is a suggestion that it may have been coded at a pharmacy but it's not explicit, so I am unable to ascertain the quality of allocation concealment"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Available information was not clear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Available information was not clear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited participants were in the analysis.
Selective reporting (reporting bias)	Unclear risk	Result of primary outcome was not available.
Other bias	Low risk	No other obvious biases.

Anderson 1985

Methods	Randomised controlled trial. Women were randomised into 3 groups, method of randomisation not stated	
Participants	Pregnant women (20-38 years old) with constipation in their third trimester and no known medical or obstetric problems. Recruited from routine antenatal clinics in Cambridge, UK. The mean gestational age is 30.92 (28-36 weeks)	
Interventions	After 2 weeks of baseline observation the women were randomly allocated into 3 groups for 2 weeks: Group A (n = 13) - 'Fibermed', 10 g corn-based biscuit; Group B (n = 14) - 23 g wheat bran; Group C (n = 13) - no intervention. We have put Group A and Group B together as dietary fibre supplementation group (n = 27) compared with no intervention group (n = 13)	
Outcomes	Frequency of stools and a change to a softer stool consistency over 2 weeks of treatment	
Notes	Some participants were taking iron and vitamin supplements and symptomatic treatments for heartburn, but none altered their medications during the study	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly allocated into three groups"
Allocation concealment (selection bias)	Unclear risk	No information available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The fibre supplements could be eaten at any time of day, the corn-based biscuits either alone or with sweet or savoury spreads, the wheat bran mixed with cereal, casseroles or deserts" Comment: no blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The fibre supplements could be eaten at any time of day, the corn-based biscuits either alone or with sweet or savoury spreads, the wheat bran mixed with cereal, casseroles or deserts" Comment: no blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	All outcomes described in the method part were reported in the results

Anderson 1985 (Continued)

Other bias	Low risk	Baseline characteristics among participants in the 3 groups were comparable. No other obvious biases

Greenhalf 1973

Methods	Randomised controlled trial. Women randomised into 4 groups, method not stated
Participants	Constipated women attending the antenatal clinic at Kingston Hospital, UK and constipated puerperal breast-feeding women delivered in the obstetric unit. 175 women recorded as being entered, but data only available for 140 (35 in each group)
Interventions	The participants were offered 1 of the 4 laxatives. There were 2 different stimulant laxatives (senokot and normax) and 2 different bulk-forming laxatives (normacol standard and normacol special). Senokot, 2 tablets daily, consists of 7 mg of standard senna (n = 35). Normax, 2 capsules a day, contains 60 mg of dioctyl sodium sulphosuccinate and 50 mg of dihydroxyanthraquinone (n = 35). Normacol standard, 2 teaspoonfuls a day, contains sterculia B.P.C. and frangula B.P.C. (n = 35). Normacol special, 2 teaspoonfuls a day, contains sterculia B.P.C. (n = 35)
Outcomes	Improvement in constipation, abdominal discomfort, diarrhoea and women's satisfaction
Notes	For the quantitative analysis, group 1 and 2 were combined as stimulant laxatives and groups 3 and 4 as bulk-forming laxatives. This review included only pregnant women

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information available.
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization of laxative used was achieved by random distribution by the nurse in charge of the antenatal clinic"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The drugs did not have an identical appearance, flavour or taste"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited participants were in the analysis.

Greenhalf 1973 (Continued)

Selective reporting (reporting bias)	Low risk	All outcomes described in the method were reported in the result
Other bias	Low risk	No other obvious bias.

Gregersen 1985

Methods	Double-blind randomised trial in Copenhagen, Denmark. Feb 1980 - Aug 1981	
Participants	Pregnant women 20-36 weeks' gestation, with constipation. Outpatients	
Interventions	Arm 1: Dumovital fibre tablets (n =133) - 2 initial weeks with no tablets, 3rd week 3 per day, 4th week 6 per day, weeks 5-9 9 tablets per day Arm 2: placebo tablets (n = 117) according to regimen above.	
Outcomes	Number of bowel movements in a 14-day period.	
Notes	This trial contributed no usable data to the review. Original publication in Danish, Jan 1995. Tables in the original Danish publication are in English	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described. Trial described as randomised and double blind
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial described as blinded. Blinding may have been achieved if tablets were similar in appearance. Women also took tablets in the community, so there would be little chance of coming across the alternate tablet
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcomes were self-reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	140 of 250 randomised failed to complete the study. Reasons for all women are stated, including side-effects of treatment (diarrhoea). However, these outcomes are only reported for women leaving the study, and so we did not use these data

Gregersen 1985 *(Continued)*

Selective reporting (reporting bias)	High risk	Primary outcome is reported, but side-effects reported only for women leaving the study
Other bias	High risk	Data for primary outcome of number of bowel movements reported in graph form only with no averages per randomised group presented

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Browne 1957	Participants were not only pregnant women. Separate information for pregnant women only was not available
Ghahramani 2013	This study did not examine treatment of constipation. The study investigated whether giving pregnant women Psyllium herbal laxative powder prevented constipation, haemorrhoids and anal fissure during pregnancy

DATA AND ANALYSES

Comparison 1. Stimulant laxatives versus bulk-forming laxatives

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in constipation	1	140	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.21, 2.09]
2 Abdominal discomfort	1	140	Risk Ratio (M-H, Fixed, 95% CI)	2.33 [1.15, 4.73]
3 Diarrhoea	1	140	Risk Ratio (M-H, Fixed, 95% CI)	4.5 [1.01, 20.09]
4 Women's satisfaction	1	140	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.77, 1.46]

Comparison 2. Stimulant laxatives versus bulk-forming laxatives (Sensitivity analysis: Senokot and Normax data separated)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in constipation	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Senokot	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [1.03, 2.26]
1.2 Normax	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [1.13, 2.41]
2 Abdominal discomfort	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Senokot	1	70	Risk Ratio (M-H, Fixed, 95% CI)	2.2 [0.85, 5.68]
2.2 Normax	1	70	Risk Ratio (M-H, Fixed, 95% CI)	2.5 [0.87, 7.22]
3 Diarrhoea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Senokot	1	70	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.62, 40.64]
3.2 Normax	1	70	Risk Ratio (M-H, Fixed, 95% CI)	4.0 [0.47, 34.02]
4 Women's satisfaction (rated as good or acceptable)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Senokot	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.62, 1.62]
4.2 Normax	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.72, 1.71]

Comparison 3. Fibre supplementation versus no intervention

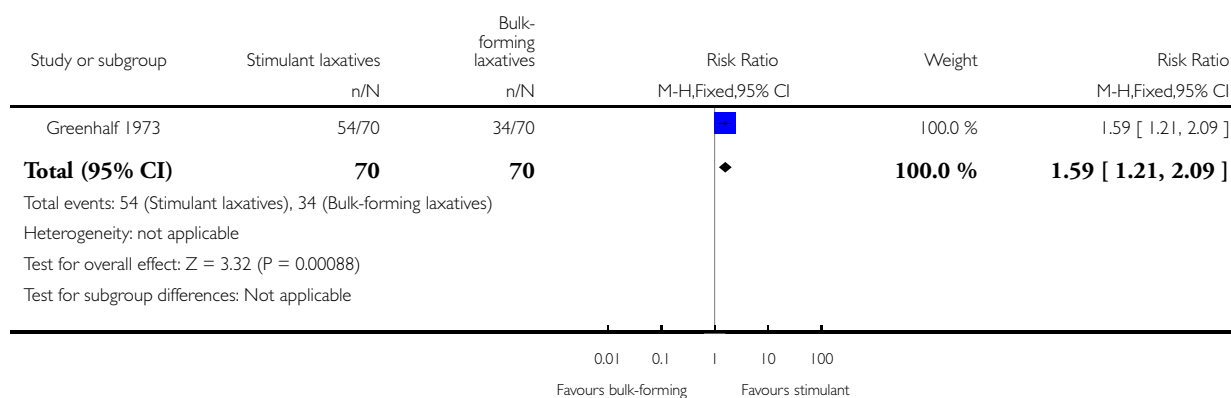
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of stools (per week)	1	40	Mean Difference (IV, Fixed, 95% CI)	2.24 [0.96, 3.52]

Analysis 1.1. Comparison 1 Stimulant laxatives versus bulk-forming laxatives, Outcome 1 Improvement in constipation.

Review: Interventions for treating constipation in pregnancy

Comparison: 1 Stimulant laxatives versus bulk-forming laxatives

Outcome: 1 Improvement in constipation

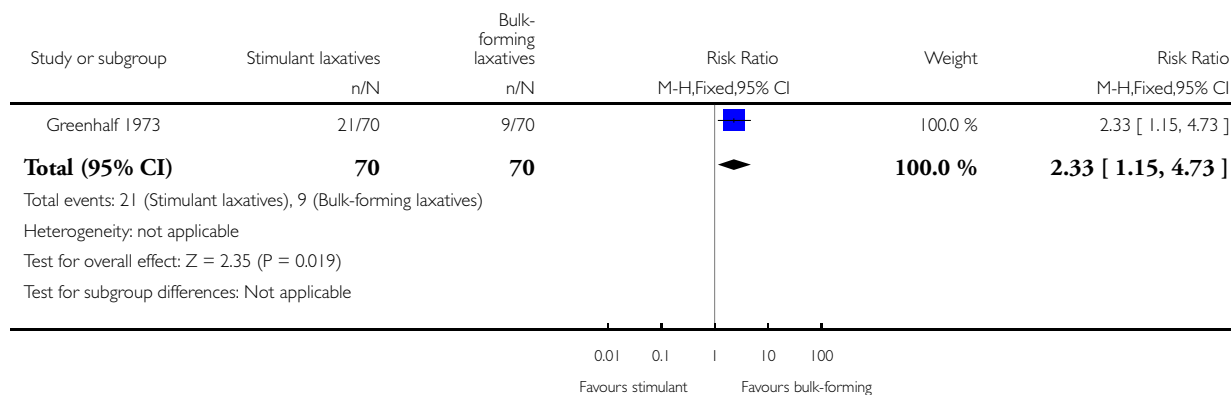


Analysis 1.2. Comparison 1 Stimulant laxatives versus bulk-forming laxatives, Outcome 2 Abdominal discomfort.

Review: Interventions for treating constipation in pregnancy

Comparison: 1 Stimulant laxatives versus bulk-forming laxatives

Outcome: 2 Abdominal discomfort

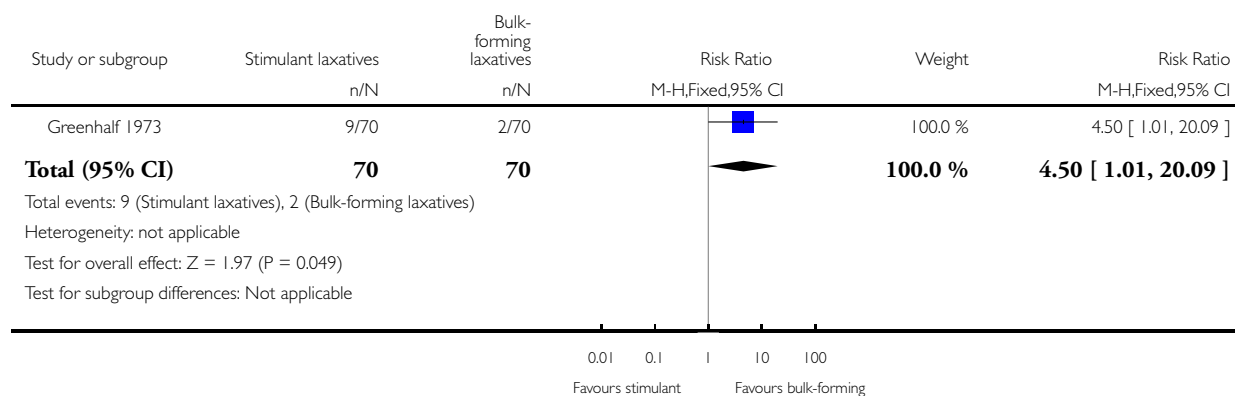


Analysis 1.3. Comparison 1 Stimulant laxatives versus bulk-forming laxatives, Outcome 3 Diarrhoea.

Review: Interventions for treating constipation in pregnancy

Comparison: 1 Stimulant laxatives versus bulk-forming laxatives

Outcome: 3 Diarrhoea

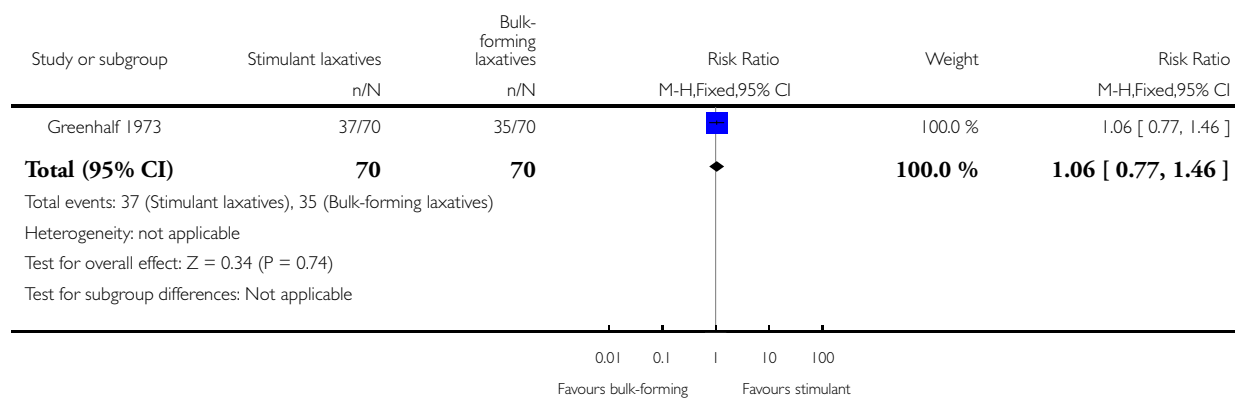


Analysis 1.4. Comparison 1 Stimulant laxatives versus bulk-forming laxatives, Outcome 4 Women's satisfaction.

Review: Interventions for treating constipation in pregnancy

Comparison: 1 Stimulant laxatives versus bulk-forming laxatives

Outcome: 4 Women's satisfaction

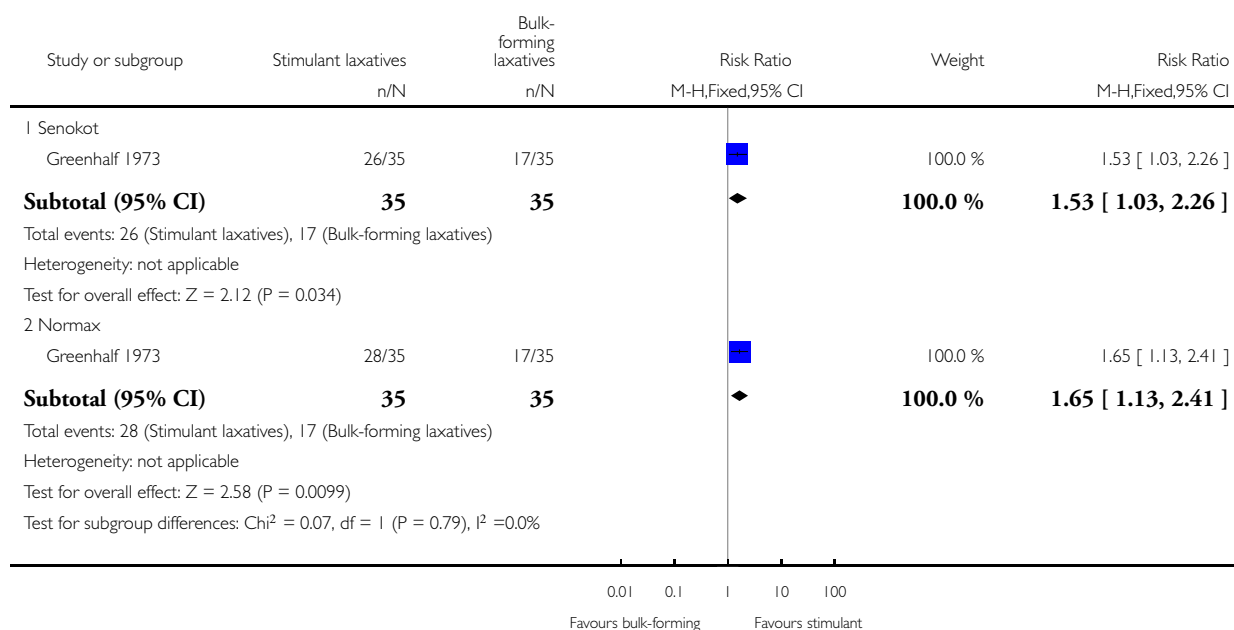


Analysis 2.1. Comparison 2 Stimulant laxatives versus bulk-forming laxatives (Sensitivity analysis: Senokot and Normax data separated), Outcome 1 Improvement in constipation.

Review: Interventions for treating constipation in pregnancy

Comparison: 2 Stimulant laxatives versus bulk-forming laxatives (Sensitivity analysis: Senokot and Normax data separated)

Outcome: 1 Improvement in constipation

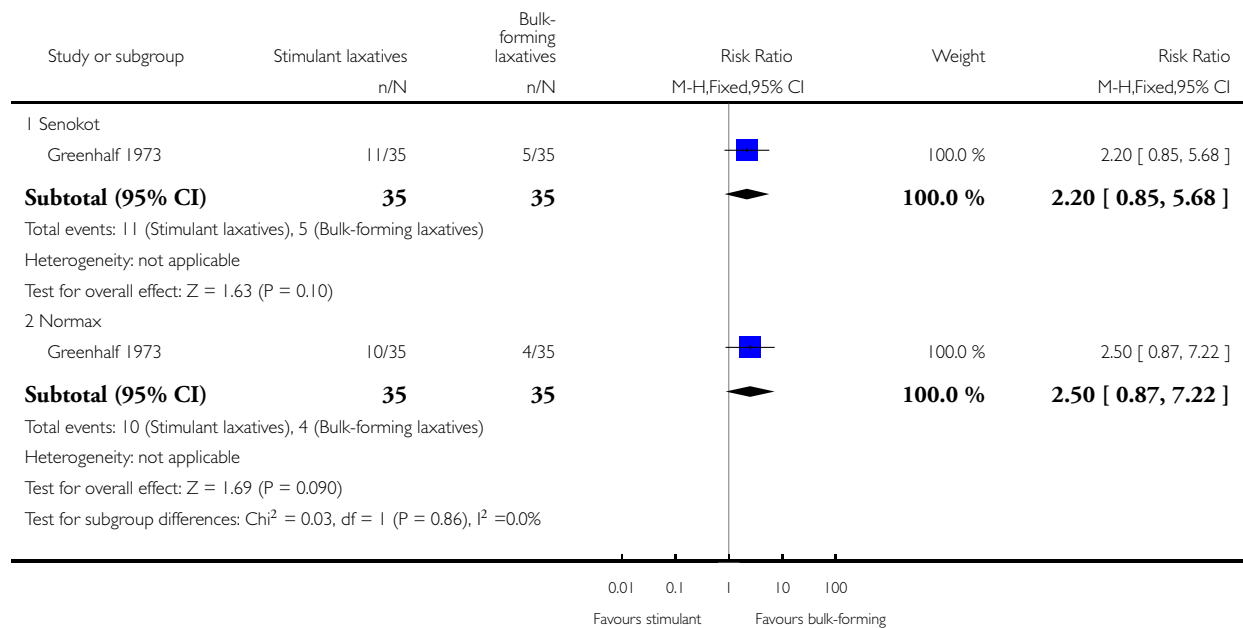


Analysis 2.2. Comparison 2 Stimulant laxatives versus bulk-forming laxatives (Sensitivity analysis: Senokot and Normax data separated), Outcome 2 Abdominal discomfort.

Review: Interventions for treating constipation in pregnancy

Comparison: 2 Stimulant laxatives versus bulk-forming laxatives (Sensitivity analysis: Senokot and Normax data separated)

Outcome: 2 Abdominal discomfort

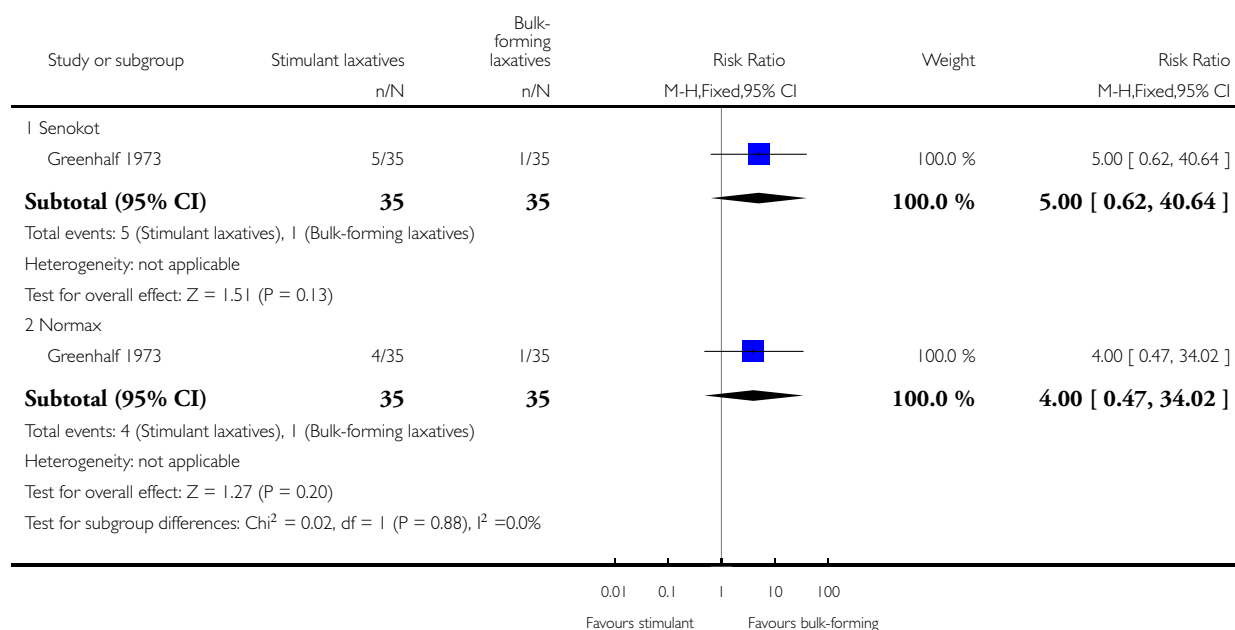


Analysis 2.3. Comparison 2 Stimulant laxatives versus bulk-forming laxatives (Sensitivity analysis: Senokot and Normax data separated), Outcome 3 Diarrhoea.

Review: Interventions for treating constipation in pregnancy

Comparison: 2 Stimulant laxatives versus bulk-forming laxatives (Sensitivity analysis: Senokot and Normax data separated)

Outcome: 3 Diarrhoea

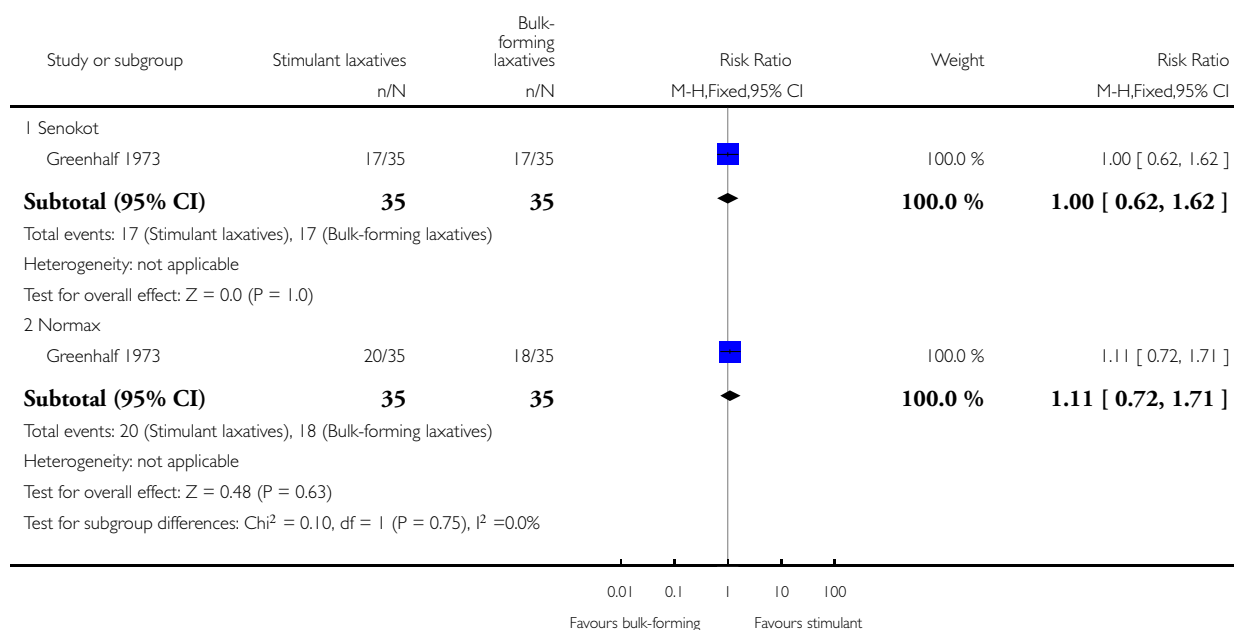


Analysis 2.4. Comparison 2 Stimulant laxatives versus bulk-forming laxatives (Sensitivity analysis: Senokot and Normax data separated), Outcome 4 Women's satisfaction (rated as good or acceptable).

Review: Interventions for treating constipation in pregnancy

Comparison: 2 Stimulant laxatives versus bulk-forming laxatives (Sensitivity analysis: Senokot and Normax data separated)

Outcome: 4 Women's satisfaction (rated as good or acceptable)

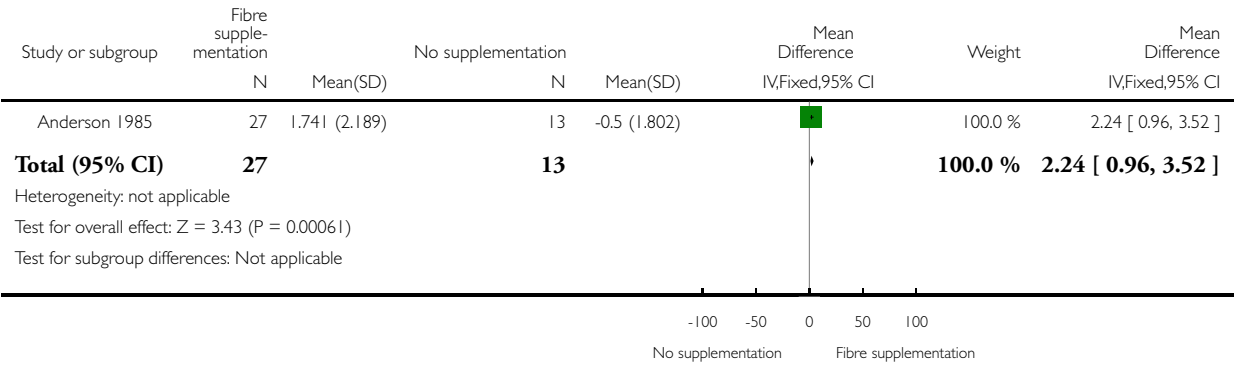


Analysis 3.1. Comparison 3 Fibre supplementation versus no intervention, Outcome 1 Frequency of stools (per week).

Review: Interventions for treating constipation in pregnancy

Comparison: 3 Fibre supplementation versus no intervention

Outcome: 1 Frequency of stools (per week)



ADDITIONAL TABLES

Table 1. Percent change in stool consistency

	Fibermed	Bran	Untreated
Hard	-14	-11	-2
Normal	5	10	0
Loose	6	0	2

Extracted from figure 2 of [Anderson 1985](#).

APPENDICES

Appendix I. Search terms

ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) (7 January 2015)
constipation AND pregnancy

WHAT'S NEW

Last assessed as up-to-date: 30 April 2015.

Date	Event	Description
4 November 2015	Amended	We included one trial in our comparison of stimulation laxatives versus bulk-forming laxatives (comparison 1) - the trial contains four arms (two different bulk-forming laxatives and two different stimulant laxatives [Senokot and Normax]). It has come to our attention that Normax (dioctyl sodium sulphosuccinate and dihydroxy anthraquinone) is no longer used for the treatment of constipation in pregnant women (and the package information advises that it should not be used during pregnancy or breastfeeding). We have highlighted this in the review and carried out a sensitivity analysis (comparison 2) with the data for Senokot and Normax presented separately

CONTRIBUTIONS OF AUTHORS

Phassawan Rungsiprakarn developed the review. Malinee Laopaiboon, Pisake Lumbiganon and Ussanee Sangkomkarnhang edited and commented on the review. Jeremy Pratt provided feedback and suggested edits in response to final editorial comments. All authors approved the final version for publication.

DECLARATIONS OF INTEREST

Phassawan Rungsiprakarn: none known.

Malinee Laopaiboon: none known.

Ussanee S Sangkomkarnhang: none known.

Pisake Lumbiganon: none known.

Jeremy J Pratt: none known.

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Internal sources

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Logistical support

- Faculty of Public Health, Khon Kaen University, Thailand.

Logistical support

- Thai Cochrane Network, Thailand.

Technical support

External sources

- Thailand Research Fund/Distinguished professor award, Thailand.

Basic honorarium and travel expenses for contact person

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

A new primary outcome has been added at the full review stage: improvement in constipation. This outcome was not prespecified in our published protocol ([Rungsiprakarn 2014](#)). The other prespecified primary outcomes (pain on defecation, frequency of stool, and consistency of stool) are components of constipation. It became obvious during the review process that studies report changes in symptoms in different ways, as such, to capture all data available, it was essential that the primary outcomes were altered. Furthermore, this broader banner encapsulates a more woman-centred understanding of constipation in pregnancy.

During the review process we found that all four potential included studies had unclear sequence generation, we were not clear whether they were randomised controlled trials (RCTs) or quasi-RCTs. We therefore added quasi-RCTs to the eligibility criteria.

In our comparison of stimulant laxatives versus bulk-forming laxatives (comparison 1) we included data from a trial with four treatment arms (two stimulant laxatives [Senokot and Normax] and two different bulk-forming laxatives). However, one of the stimulant laxatives, Normax (dioctyl sodium sulphosuccinate and dihydroxy anthraquinone) is no longer used for the treatment of constipation in pregnant women (and package information advises that it should not be used during pregnancy or breastfeeding). We therefore carried out a sensitivity analysis (not prespecified in our protocol) with the data for Senokot and Normax presented separately.

INDEX TERMS

Medical Subject Headings (MeSH)

Constipation [*therapy]; Dietary Fiber [*therapeutic use]; Laxatives [*therapeutic use]; Pregnancy Complications [*therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Female; Humans; Pregnancy



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Interval debulking surgery for advanced epithelial ovarian cancer (Review)

Tangjitgamol S, Manusirivithaya S, Laopaiboon M, Lumbiganon P, Bryant A

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	2
OBJECTIVES	4
METHODS	4
Figure 1.	6
Figure 2.	7
RESULTS	8
Figure 3.	9
DISCUSSION	13
AUTHORS' CONCLUSIONS	14
ACKNOWLEDGEMENTS	14
REFERENCES	15
CHARACTERISTICS OF STUDIES	18
DATA AND ANALYSES	26
Analysis 1.1. Comparison 1 IDS vs chemotherapy only, Outcome 1 Overall survival.	27
Analysis 1.2. Comparison 1 IDS vs chemotherapy only, Outcome 2 Progression-free survival.	28
Analysis 1.3. Comparison 1 IDS vs chemotherapy only, Outcome 3 Toxic reactions to chemotherapy.	28
Analysis 1.4. Comparison 1 IDS vs chemotherapy only, Outcome 4 Peripheral neuropathy of grade 2 or higher.	29
Analysis 1.5. Comparison 1 IDS vs chemotherapy only, Outcome 5 Grade 3 or 4 gastrointestinal adverse events.	29
Analysis 1.6. Comparison 1 IDS vs chemotherapy only, Outcome 6 Grade 4 pulmonary adverse events.	30
Analysis 1.7. Comparison 1 IDS vs chemotherapy only, Outcome 7 Grade 4 cardiovascular adverse events.	30
APPENDICES	30
WHAT'S NEW	32
HISTORY	32
CONTRIBUTIONS OF AUTHORS	33
DECLARATIONS OF INTEREST	33
SOURCES OF SUPPORT	33
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	33
INDEX TERMS	34

Interval debulking surgery for advanced epithelial ovarian cancer

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ABSTRACT

Background

Interval debulking surgery (IDS), following induction or neoadjuvant chemotherapy, may have a role in treating advanced epithelial ovarian cancer (stage III to IV) where primary debulking surgery is not an option.

Objectives

To assess the effectiveness and complications of IDS for women with advanced stage epithelial ovarian cancer.

Search methods

We searched the Cochrane Gynaecological Cancer Group's Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 6, MEDLINE and EMBASE for the original review in to June 2012. We updated the searches in June 2009, 2012 and 2015 for the review updates.

Selection criteria

Randomised controlled trials (RCTs) comparing survival of women with advanced epithelial ovarian cancer, who had IDS performed between cycles of chemotherapy after primary surgery with survival of women who had conventional treatment (primary debulking surgery and adjuvant chemotherapy).

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. Searches for additional information from study authors were attempted. We performed meta-analysis of overall and progression-free survival (PFS), using random-effects models.

Main results

Three RCTs randomising 853 women, of whom 781 were evaluated, met the inclusion criteria. Meta-analysis of three trials for overall survival (OS) found no statistically significant difference between IDS and chemotherapy alone (hazard ratio (HR) = 0.80, 95% confidence interval (CI) 0.61 to 1.06, I^2 = 58%). Subgroup analysis for OS in two trials, where the primary surgery was not performed by gynaecologic oncologists or was less extensive, showed a benefit of IDS (HR = 0.68, 95% CI 0.53 to 0.87, I^2 = 0%). Meta-analysis of two trials for PFS found no statistically significant difference between IDS and chemotherapy alone (HR = 0.88, 95% CI 0.57 to 1.33, I^2 = 83%). Rates of toxic reactions to chemotherapy were similar in both arms (risk ratio = 1.19, 95% CI 0.53 to 2.66, I^2 = 0%), but little information was available for other adverse events or quality of life (QoL).

Authors' conclusions

We found no conclusive evidence to determine whether IDS between cycles of chemotherapy would improve or decrease the survival rates of women with advanced ovarian cancer, compared with conventional treatment of primary surgery followed by adjuvant chemotherapy. IDS appeared to yield benefit only in women whose primary surgery was not performed by gynaecologic oncologists or was less extensive. Data on QoL and adverse events were inconclusive.

PLAIN LANGUAGE SUMMARY

Interval debulking surgery for advanced epithelial ovarian cancer

Ovarian cancer frequently presents at an advanced stage so it may not be possible to remove all tumours during surgery. Several cycles of chemotherapy are generally given after primary surgery. Secondary surgery, performed after a few cycles of chemotherapy before further cycles of chemotherapy, is called interval debulking surgery (IDS). This review compares the survival of women with advanced epithelial ovarian cancer, who had IDS performed between cycles of chemotherapy after primary surgery, with survival of women who had conventional treatment (primary debulking surgery and adjuvant chemotherapy). It found similar survival rates in women who did and did not receive IDS. Not enough information about adverse effects was available. Information on quality of life of the women was also inconclusive.

BACKGROUND

Ovarian cancer is the fourth most common gynaecologic cancer among women, and is the third leading cause of death in women with gynaecological malignancies. Approximately 238,700 new cases and 151,900 deaths of ovarian occurred worldwide in 2012 (Torre 2015). Primary surgery is the mainstay of treatment for ovarian cancer, followed by adjuvant chemotherapy to destroy any gross or microscopic residual tumour cells.

Primary ovarian cancer surgery is performed to achieve optimal cytoreduction, as the amount of residual tumour is one of the most important prognostic factors for survival of women with epithelial ovarian cancer (Griffiths 1975; Hoskin 1994; Bristow 2002). The definition of optimal debulking surgery has changed over the past 30 years from the residual tumour sized not more than 1 to 2 cms to no macroscopic disease (Griffiths 1975; Elattar 2011). An optimal surgical procedure required for advanced stage disease (III to IV) is not always possible, especially in women whose

diseases are extensive. Such surgery can be complicated, requiring extensive bowel resection and major blood loss, with a high risk of morbidity. Another obstacle to extensive primary surgery lies in the women's medical condition, e.g. poor projected performance status or medical contraindications.

Induction chemotherapy can play an alternative role in these circumstances. The term generally describes the administration of chemotherapy to reduce tumour size, allowing further surgery. The term 'neoadjuvant chemotherapy' (NAC) is more specific in that it describes the administration of chemotherapy when primary debulking surgery is not feasible, and only a biopsy is done for histologic diagnosis. However, the two terms are sometimes used interchangeably. In this review, if chemotherapy administration does not fit the definition of NAC, we will use the term induction chemotherapy.

When a few cycles of chemotherapy are administered with some tumour response, secondary surgery may be possible before fur-

ther chemotherapy is considered. This secondary surgery between the courses of chemotherapy is called interval debulking surgery (IDS). Although the optimal timing of IDS has not been agreed, it is usually performed after two to four cycles of chemotherapy. A longer interval between primary surgery and IDS (with more cycles of chemotherapy) could result in the chemotherapy selectively destroying chemosensitive tumour cells, leaving chemoresistant clones. Many retrospective or prospective non-randomised trials report the beneficial effects of NAC or induction chemotherapy after inoperable advanced ovarian cancer or in those with gross residual diseases, respectively. Chemotherapy may increase the number of women suitable for secondary surgery (IDS); many authors report the rates of optimal resection in IDS after induction chemotherapy ranging from 77% to 94% (Lawton 1989; Jacob 1991; Surwit 1996; Ansquer 2001; Kuhn 2001; Chan 2003; Morice 2003; Giannopoulos 2006; Lee 2006).

Another potential benefit of IDS after NAC or induction chemotherapy, compared to aggressive primary debulking surgery, as reported in retrospective (Lawton 1989; Morice 2003) and prospective (Giannopoulos 2006) cohort studies, may be lower morbidity, e.g. less blood loss, requirement of intensive care unit admission, and duration of hospital stay due to the tumours being smaller. However, this was not found in another study (Kuhn 2001). The quality of life (QoL) of women treated with IDS after NAC was also reported in one study to be better than for those who had conventional treatment (primary debulking surgery followed by a complete and continual cycle of adjuvant chemotherapy) (Chan 2003). By removing the smaller size tumour masses induced by chemotherapy, IDS would facilitate the response of the residual tumours (if any) or of the microscopic lesions to subsequent chemotherapy.

Unlike the advantages for resectability and response rates which were demonstrated in most studies, there is still conflicting evidence from various studies regarding the survival benefit of IDS after chemotherapy compared to conventional treatment. Most studies of IDS after NAC or induction chemotherapy are non-randomised and retrospective in nature. Many of them show that the survival rates of women who underwent IDS, after suboptimal primary surgery followed by chemotherapy, were similar to those of women who had primary debulking surgery (Jacob 1991; Surwit 1996; Schwartz 1999; Kayikcioglu 2001; Morice 2003; Shibata 2003; Loizzi 2005). Only a few studies reported significantly longer median survival of women who had IDS after chemotherapy than of those who had conventional treatment of primary surgery and adjuvant chemotherapy (Vergote 1998; Kuhn 2001), and even fewer studies showed an inferior result for IDS than for optimal primary cytoreduction (Fanfani 2003). This conflicting result on the survival benefit of IDS may depend on various characteristics of the women and their disease, e.g. extent of residual tumour after primary surgery or IDS, tumour response after induction chemotherapy and prior to IDS, etc. (Jacob 1991;

Vergote 1998; Kuhn 2001; Fanfani 2003; Mazzeo 2003).

We are aware of three major randomised controlled trials (RCTs) (Redman 1994; Van der Burg 1995; Rose 2004) which have been conducted to evaluate the survival benefit of IDS in ovarian cancer. These trials did not agree on the benefit of survival outcomes for women with IDS. Redman 1994 and Rose 2004 showed similar survival rates between women who had IDS and those who had conventional treatment, while Van der Burg 1995 showed significantly longer survival in the IDS group which was still present after a 10-year follow-up.

One previous meta-analytical study (Bristow 2006) and two systematic reviews (Bristow 2007; Morrison 2012) addressed the question of whether women with advanced ovarian cancer should have primary surgery before or after chemotherapy. The first meta-analytical study reviewed the role of platinum-based NAC and IDS for advanced ovarian cancer, involving 835 women from 51 studies (Bristow 2006). The result showed that the survival of women who had NAC after an attempt at primary surgery was inferior to those who had primary surgery. However, the review included only phase I to II and retrospective studies. The other systematic review of NAC or induction chemotherapy and IDS in advanced ovarian cancer was published in 2007 (Bristow 2007). The review included the three major RCTs, six non-randomised studies, and another 26 retrospective and phase I or II studies. The authors categorised the studies into three groups according mainly to the survival outcomes of the women in the NAC or induction chemotherapy/IDS arm compared to the conventional arm: inferior survival outcome by NAC; no significant difference; and those with limited validation of inclusion criteria for NAC. The results from these studies were simply described and tabulated without a meta-analysis for survival. A Cochrane systematic review was conducted on the role of NAC on overall survival of women with ovarian cancer (Morrison 2012), and included only one large and high quality randomised trial (Vergote 2010), of 632 eligible women with stage IIIC or IV ovarian cancer allocated either to NAC followed by IDS or to primary debulking surgery (PDS) followed by chemotherapy. Although the completely resection rate was higher in the NAC group (52% versus 20%), no significant differences in overall survival (OS) and progression-free survival (PFS) were found between the study groups. The review authors concluded that NAC was a reasonable alternative in women with bulky stage IIIC to IV ovarian cancer.

The objective of these systematic reviews and meta-analyses was to evaluate the use of NAC in lieu of primary surgery, which is different from the aim of our review which focuses on the role of repeated surgery (IDS) after primary surgery which had been attempted but resulted in suboptimal surgery.

We found only one previous meta-analysis which reviewed the role of IDS after NAC in advanced ovarian cancer (Elit 1995). The authors of that review identified 33 publications and included

three RCTs and three historical cohort trials. Homogeneity testing was not statistically significant by the Breslow-Day method. Significant survival benefit from IDS was identified by a Mantel-Haenszel odds ratio of 0.5 ($P = 0.02$).

Since there were potentially intrinsic biases of participant selection and variations in several factors, such as chemotherapeutic agents or cycles of administration in many retrospective or phase I and II studies, together with conflicting data from the RCTs, no definite conclusion about the advantage of IDS after attempted primary surgery could be drawn. Hence, a thorough systematic review of this subject is warranted, focusing only on high quality data or trials, to give a stronger assessment of the use of IDS in advanced epithelial ovarian cancers.

OBJECTIVES

To assess the effectiveness and complications of interval debulking surgery (IDS) for women with advanced stage epithelial ovarian cancer.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Women with advanced stage epithelial ovarian cancer who have a confirmed pathological diagnosis from primary surgery which was suboptimal, with residual tumours of more than 1 to 2 cms. Primary surgical procedures include tumour biopsy, tumour removal, or standard surgical staging for epithelial ovarian cancer.

Types of interventions

Treatment: Interval debulking surgery (IDS), defined as secondary surgery which is performed after two to four cycles of neoadjuvant chemotherapy (NAC) or induction chemotherapy, to remove the bulk of the tumour, and followed by adjuvant chemotherapy of the same type.

Control: Adjuvant chemotherapy only.

Types of outcome measures

Primary outcomes

- Overall survival (OS): Survival until death from all causes. Survival was assessed from the time when women were enrolled in the study.

Secondary outcomes

- Progression-free survival (PFS).
- Adverse events.
- Quality of life (QoL), measured using a scale that had been validated through reporting of norms in a peer-reviewed publication.

Search methods for identification of studies

We sought articles in all languages, and carried out translations where necessary.

Electronic searches

See: [Cochrane Gynaecological Cancer Group](#) methods used in reviews.

We ran searches on the following databases: Cochrane Gynaecological Cancer Group's Specialised Register (CGCSR) to June 2008, the Cochrane Central Register of Controlled Trials (CENTRAL) 2008, Issue 2, MEDLINE from January 1966 to June 2008, and EMBASE from January 1980 to June 2008. We extended the second wave of updated searches to July 2009, CENTRAL 2009, Issue 2, MEDLINE Ovid to June week 4 2009, EMBASE to 2009 week 27. We also extended the searches in June 2012 and again in June 2015 (see [Appendix 1](#); [Appendix 2](#); [Appendix 3](#)).

We identified all relevant articles found on PubMed, and used the 'related articles' feature to conduct a further search for newly published articles.

Searching other resources

Unpublished and grey literature

We searched Metaregister, Physicians Data Query, www.controlled-trials.com/rct, www.clinicaltrials.gov and www.cancer.gov/clinicaltrials and Gynaecologic Oncologists of Canada (<http://www.g-o-c.org>) for ongoing trials. We then contacted the main investigators of any relevant ongoing trials for further information, as well as the major co-operative trials groups active in this area.

Reference lists and correspondence

We checked the citation lists of included trials to identify further study reports. We also contacted authors of all trials and/or reviews relevant to this topic to request information on any similar trials. We invited colleagues, collaborators and other experts in the field to identify missing or unreported trials.

Data collection and analysis

Selection of studies

We downloaded all titles and abstracts retrieved by electronic searching to a reference management database (Endnote), where two review authors (ST and SM) removed duplicates and independently examined the remaining references. We excluded those studies which clearly did not meet the inclusion criteria, and obtained copies of the full text of potentially relevant references. We evaluated English abstracts of non-English studies, and acquired full text versions of eligible studies and had them translated. The two authors (ST and SM) independently assessed the eligibility of all retrieved papers, resolving disagreements by discussion.

Data extraction and management

For included studies, we abstracted data as recommended in Chapter 7 of the [Cochrane Handbook](#).

We collected data on authors, year of publication, journal citation, country, setting, inclusion and exclusion criteria, study design and methodology, study population (total number enrolled, participant characteristics, age, size and number of residual tumours after primary surgery, performance status, stage, histology, size and number of residual tumours before and after IDS), interventions (expertise of surgeons, type and schedule of chemotherapy, duration of the treatment), risk of bias, duration of follow-up and outcomes (OS, PFS, QoL and adverse events). We also recorded the following information for each outcome of interest:

- outcome definition;
- unit of measurement (if relevant);
- for scales: upper and lower limits, and whether high or low score is good;
- results: number of participants allocated to each intervention group;
- sample size; missing participants.

We extracted outcome data as follows:

- for time to event (OS) data, we extracted the log of the hazard ratio [log(HR)] and its standard error from trial reports; if these were not reported, we attempted to estimate them from other reported statistics using the methods of [Parmar 1998](#);
- for dichotomous outcomes (e.g. adverse events), we extracted the number of participants in each group who experienced the outcome of interest and the number assessed at end point, in order to estimate a risk ratio (RR).

We recorded both unadjusted and adjusted statistics, if reported. Where possible, all data extracted were those relevant to an intention-to-treat (ITT) analysis, in which participants were analysed in the groups to which they were originally assigned.

We noted the time points at which outcomes were collected and reported.

Two review authors (ST and SM) independently extracted data, using a form specifically designed for this review. We resolved disagreements by discussion, or by recourse to a third author (PL).

Assessment of risk of bias in included studies

We assessed the risk of bias in the included RCTs using the Cochrane Collaboration's tool and the criteria specified in chapter 8 of the [Cochrane Handbook](#). This includes assessment of:

- sequence generation;
- allocation concealment;
- blinding (of outcome assessors only, since it was not possible to blind either participants or physicians to the assigned treatment);
- incomplete outcome data: we coded the satisfactory level of loss to follow-up for each outcome as
 - Yes, if fewer than 20% of women were lost to follow-up and reasons for loss were similar in both treatment arms;
 - No, if more than 20% of women were lost to follow-up or reasons for loss differed between treatment arms;
 - Unclear, if loss to follow-up was not reported;
- selective reporting of outcomes;
- other possible sources of bias.

Two review authors (ST and SM) independently applied the risk of bias tool, resolving differences by discussion or by appeal to a third author (PL). [Figure 1](#), [Figure 2](#). We have interpreted the results of our meta-analyses in the light of the findings of the risk of bias assessments.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

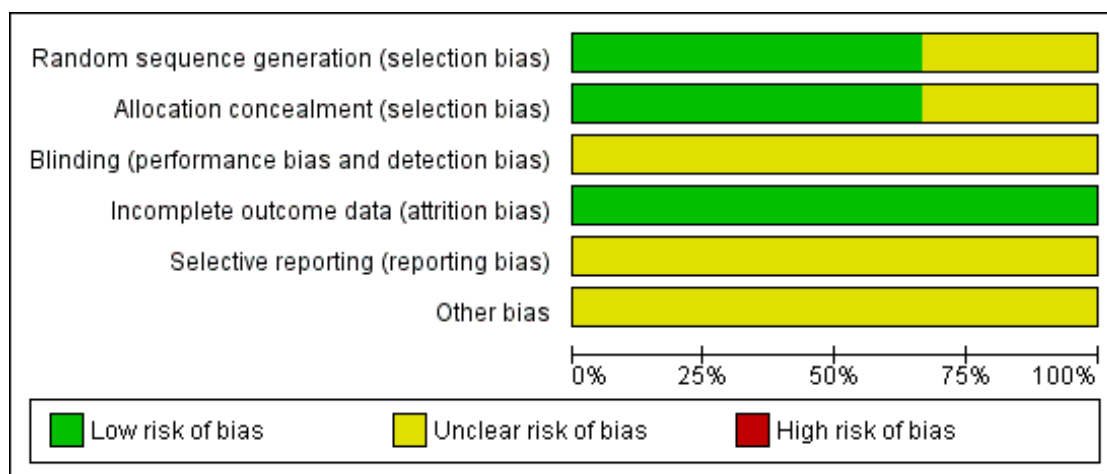


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Redman 1994	+	+	?	+	?	?
Rose 2004	?	?	?	+	?	?
Van der Burg 1995	+	+	?	+	?	?

Measures of treatment effect

We used the following measures of the effect of treatment:

- for time to event data, we have used the hazard ratio (HR), where possible;
- for dichotomous outcomes, we have used the risk ratio (RR).

Dealing with missing data

We attempted to extract data on the outcomes only among participants who were assessed at end point. We did not impute missing outcome data; if only imputed outcome data were reported, we

contacted trial authors to request data on the outcomes only for participants who were actually assessed.

Assessment of heterogeneity

We assessed heterogeneity between studies by visual inspection of forest plots, by estimation of the I^2 statistic, i.e. the percentage of heterogeneity between trials which could not be ascribed to sampling variation (Higgins 2003), by a formal statistical test of the significance of the heterogeneity (Deeks 2001), and if possible by subgroup analyses (see below). If there was evidence of substantial heterogeneity, we investigated and reported the possible reasons.

Assessment of reporting biases

There were too few studies which met our inclusion criteria to allow us to assess reporting bias.

Data synthesis

We pooled the findings of the included studies in meta-analyses, using adjusted summary statistics where available, and otherwise unadjusted results.

- For time-to-event data, we produced and pooled HRs using the generic inverse variance facility of Review Manager 5.
- For any dichotomous outcomes, we calculated the RR for each study and then pooled them.

We used random-effects models with inverse variance weighting for all meta-analyses ([DerSimonian 1986](#)).

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses where possible, grouping trials by the expertise of the surgeons (gynaecological oncologist, gynaecologist, general surgeon).

Factors such as age, stage, type of intervention, length of follow-up, adjusted/unadjusted analysis were considered in interpretation of any heterogeneity.

Sensitivity analysis

There were too few included studies in this review to perform meaningful sensitivity analyses.

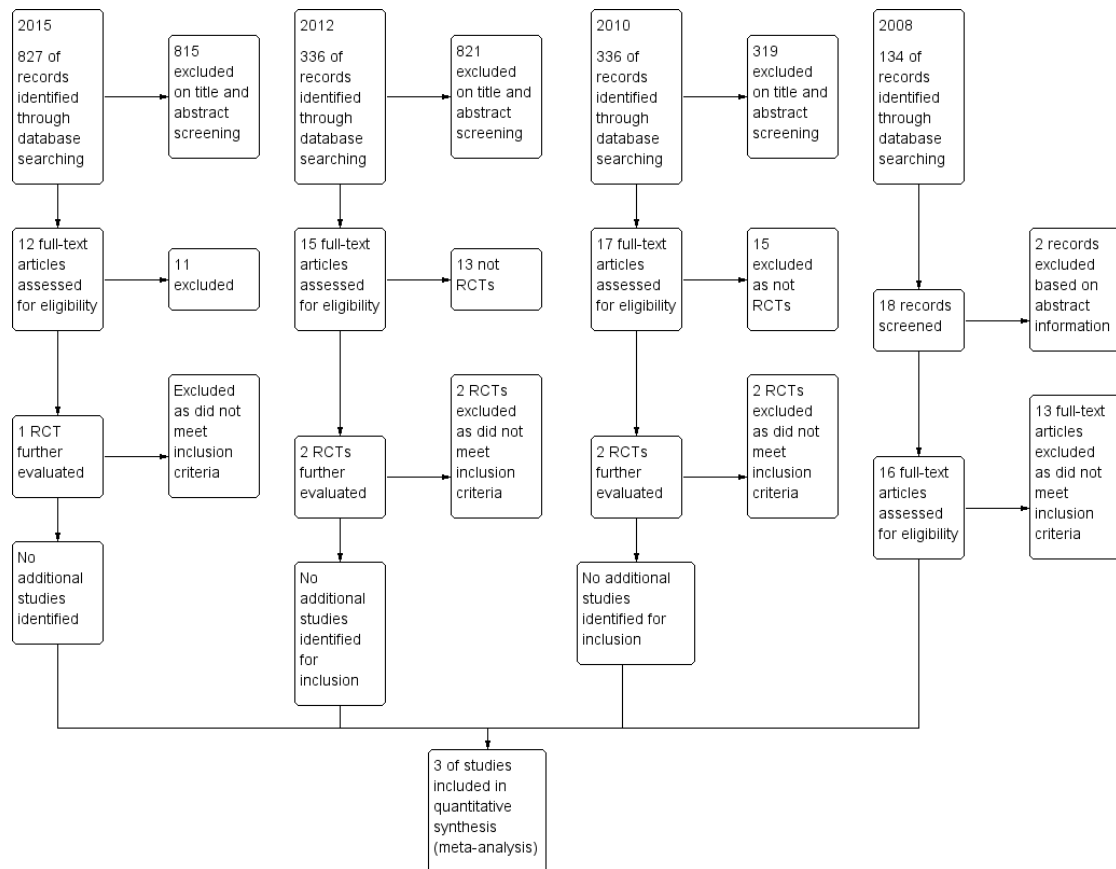
RESULTS

Description of studies

Results of the search

We examined the titles and abstracts of 134 references identified by the original search, and considered that 18 studies were potentially relevant to this review. Two studies were readily excluded from the data in the abstracts ([Evdokimova 1982](#); [Kumar 2009](#)). We obtained full text articles of 16 studies, and two authors (ST and SM) assessed them independently for eligibility. Thirteen of the 16 were excluded in this process. We present reasons for exclusion in the [Characteristics of excluded studies](#) table. Three randomised controlled trials (RCTs) met all the inclusion criteria ([Redman 1994](#); [Van der Burg 1995](#); [Rose 2004](#)). The updated search in 2010 identified 336 references, of which there were 17 possibly relevant articles. Only two of these were RCTs, and both were excluded studies ([Onda 2009](#); [Vergote 2010](#)). The updated search in 2012 identified 836 references, some of which were duplicates. We identified 15 candidate articles, including two RCTs which were then excluded ([Kumar 2009](#); [Polcher 2009](#)). We updated the search again in June 2015 and an additional 827 references were identified. The preliminary sift excluded 815 of these and we identified 12 for further scrutiny. One RCT was identified but this was excluded ([Madhuri 2014](#)) ([Figure 3](#)).

Figure 3. Study flow diagram.



Included studies

All three RCTs were multicentre studies: one from the United Kingdom (UK) involved four institutions which were the referral centres for cancer care (Redman 1994); one by the European Organisation for Research and Treatment of Cancer (EORTC) involved 14 participating institutions in Europe (Van der Burg 1995), and one by the Gynecologic Oncology Group (GOG) from the United States (USA) involved more than 42 cancer centres (Rose 2004).

All three of the included trials compared interval debulking surgery (IDS) plus chemotherapy with chemotherapy only.

Median length of follow-up was reported in all three trials: 48 months (Redman 1994), 42 months (Van der Burg 1995), and 47 months (Rose 2004). Although Van der Burg and colleagues from the EORTC presented their long-term follow-up (10 years) as an oral presentation in the European Society of Gynaecological Oncology annual meeting in 2005 (Van der Burg 2005), the data were insufficient to include in our meta-analysis.

Redman 1994 supplied data relating to non-assignment of treatment as: death, disease progression, pulmonary embolus, and participant refusal. The other two trials reported only the numbers or percentages of those not undergoing surgery, but the reasons were not stated (Van der Burg 1995; Rose 2004).

All three trials reported hazard ratios (HRs) for overall survival (OS). Two trials (Van der Burg 1995; Rose 2004) used Cox regression to assess the prognostic significance of numerous covariates, including age, performance status, stage, tumour grade, response to induction chemotherapy, number of lesions, ascites, and residual diseases or size of tumours at three time points: after primary surgery, before IDS and after IDS. The definitions of optimal debulking or size of residual tumours after primary surgery varied among the trials. Optimal surgery was either defined as less than 2 cms (Redman 1994) or more than 1 cm (Van der Burg 1995; Rose 2004). Overall survival was variously calculated from the day of induction chemotherapy initiation at enrolment (Van der Burg 1995), or from the date of randomisation, which was either after primary surgery but before chemotherapy in Redman 1994, or

after three cycles of chemotherapy in [Rose 2004](#). Both the GOG and the EORTC trials reported HRs adjusted for prognostic factors; [Redman 1994](#) also reported unadjusted HRs.

[Rose 2004](#) reported the HR, adjusted for prognostic factors, for PFS data, and [Van der Burg 1995](#) presented Kaplan-Meier disease-free survival curves, from which we used Parmar's method ([Parmar 1998](#)) to estimate the HR. The definitions of response and recurrence varied among the trials: [Redman 1994](#) applied the International Union Against Cancer (UICC) criteria for response evaluation, using physical examination, imaging studies, but not CA125; the EORTC trial ([Van der Burg 1995](#)) used the World Health Organization (WHO) criteria allowing physical examination, imaging studies, and CA125; the GOG trial ([Rose 2004](#)) also used physical examination, imaging studies, and two CA125 levels two weeks apart, and defined progressive disease as an increase of at least 100 U/ml or a doubling of the nadir in those whose level did not return to baseline.

All three trials reported adverse events. However, [Redman 1994](#) and [Van der Burg 1995](#) described postoperative complications only in the IDS groups, while [Rose 2004](#) compared general adverse effects between the IDS group and the chemotherapy only (control) group.

Quality of life (QoL) was assessed only in the GOG trial, with results reported subsequently by [Wenzel 2005](#). The assessment tool used was the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) questionnaire, and treatment-specific supplemental questions at the third and sixth chemotherapy cycles and at six and 12 months after starting treatment.

Redman 1994

[Redman 1994](#), from the UK, is the first known RCT of IDS for the management of epithelial ovarian cancer. From April 1986 to February 1990, the authors randomised 86 women with stage II to IV disease, who underwent primary surgery in 25 hospitals by 40 different surgeons and had residual disease greater than 2 cms. It was not clear how experienced the 40 surgeons were, but the primary surgery had to be performed with an attempt to remove as much tumour as possible. Stage IV included only malignant pleural effusion without other evidence of distant spread or unresectable diseases. The women received chemotherapy consisting of either a regimen of cisplatin and cyclophosphamide for eight cycles or a regimen of cisplatin, doxorubicin and bleomycin for three cycles followed by an escalated dose of cyclophosphamide for up to five cycles. Either regimen was given without detailed criteria for regimen selection. The control group had only chemotherapy after primary surgery. The intervention group had chemotherapy for one to four cycles and underwent IDS, which was performed by the primary surgeon, and then received further chemotherapy. Although our inclusion criteria for this review is IDS to be performed after chemotherapy for a minimum of two cycles, this study is included because only one out of 37 women in the

IDS group had only one cycle of chemotherapy before IDS. Interval debulking surgery was not performed if there was progressive disease, stable disease, or insufficient response after three cycles.

Seven of the 86 randomised women were excluded after randomisation because primary surgery was not suboptimal. Of the remaining 79 women, 37 were in the IDS arm and 42 in the conventional arm. There were no significant differences between arms in participant or disease characteristics. Overall, 25 women (68%) in the intervention arm actually underwent IDS. The reasons for not performing IDS in 12 participants (32%) were: death or progressive disease, pulmonary embolism, and participant refusal. In the conventional arm, one woman (2%) had IDS upon request. Adverse effects of IDS were reported as perioperative death and significant postoperative complications, including deep vein thrombosis, intestinal fistulae, chest or wound infections, or postoperative ileus. Adverse effects in the chemotherapy only group were not exhaustively reported. Toxicity was reported in both treatment groups.

Van der Burg 1995

[Van der Burg 1995](#) enrolled 425 stage IIB to IV epithelial ovarian cancer patients between March 1987 and May 1993 who had undergone primary surgery and had residual disease greater than 1 cm. Their primary report described neither the extent nor the aim of primary surgery, nor the expertise of the surgeon. However, the authors provided additional data in their reply to a letter to the Editor of the New England Journal of Medicine ([Kehoe 1995](#)), and in their subsequent review article ([Van der Burg 2003](#)). They reported that the maximum effort to perform primary surgery was not attempted in all patients with different extents of debulking surgery, resulting in a high proportion of large residual tumours (more than 5 cms) after primary surgery ([Van der Burg 2003](#)).

All patients received three cycles of chemotherapy consisting of intravenous cisplatin and cyclophosphamide. Those who had response or stable diseases were randomised to undergo IDS or no IDS. Both groups would receive three more cycles of the same chemotherapy, with continuation after six cycles determined by institution policy.

Overall, 106 women were not randomised; this number consisted of 39 with progressive disease who were removed from the study, and also those who had contraindications to surgery, had died, had declined to participate in the study, were ineligible, or were lost to follow-up, and those who were still receiving induction chemotherapy.

Of 319 women randomised, 278 were evaluated (140 women who underwent surgery and 138 who did not). The two groups were well balanced with respect to stage, histologic type and grade, number and size of lesions, peritoneal carcinomatosis, ascites, and response to induction chemotherapy. The rate of optimal debulking surgery (residual tumour less than 1 cm) was 64%.

The following peri- and postoperative adverse events were reported

in the trial: bowel injury, urinary bladder injury, blood loss and postoperative fever, ileus, urinary tract infection, wound infection, deep vein thrombosis, and lung embolism.

Rose 2004

[Rose 2004](#) enrolled 550 women from June 1994 to January 2001, with stage III to IV (malignant pleural effusion or a resected anterior abdominal wall tumour) who underwent primary surgery to remove as much tumour as possible, but who still had residual disease greater than 1 cm. However, after March 1996 when the EORTC trial ([Van der Burg 1995](#)) reported a greater benefit from secondary surgery after the exclusion of patients with stage IV diseases, only those with stage III disease were included. The primary surgeons were either fellowship-trained or certified gynaecologic oncologists for 95% of participants. Those whose disease had not progressed and who had residual extraperitoneal tumour of less than 1 cm after three cycles of chemotherapy with paclitaxel and cisplatin were randomly assigned to secondary surgical cytoreduction (IDS) and further chemotherapy, or to chemotherapy alone. Overall, 102 women were not randomised; the most common reasons were: progressive disease or death in 40 women, while the remainder were either medically contra-indicated, had declined, had extraperitoneal disease greater than 1 cm, had experienced excessive delay before randomisation, or for other unspecified reasons.

A total of 448 women were randomised: 226 were allocated to IDS and 222 to chemotherapy only. Participant characteristics were well balanced between the two groups. A considerable number of women in both groups had protocol violations, including: 7% in the IDS group did not have secondary surgery, versus 3% in the chemotherapy only arm who did receive surgery; 7% and 2% in the IDS and chemotherapy only arms respectively had fewer than three cycles of additional chemotherapy; and 10% and 13% in the IDS and chemotherapy only arms respectively had non-protocol consolidation therapy before progressive disease. All randomised women were included in the analysis of OS and PFS, and were counted in the group comparisons.

We performed Cox regression for OS and PFS to evaluate the prognostic importance of: the maximal diameter of residual tumour (2.0 cms or less, 2.1 to 5.0 cms, or 5.0 cms or more) after initial surgery, age, performance status, the presence or absence of measurable disease before chemotherapy, and the size of residual tumour after IDS (less than 1 cm versus more than 1 cm).

Quality of life (QoL) of those who did and did not undergo IDS in the GOG study was evaluated and subsequently reported by [Wenzel 2005](#). The self-reported QoL was assessed in four settings, according to the Functional Assessment of Cancer Therapy-Ovarian (FACT-O), version 2-questionnaire, which consists of 33 general questions for cancer patients and 12 questions specific to those with ovarian cancer. The first evaluation was at baseline after primary surgery and the third cycle of chemotherapy, but before allo-

cation to IDS or chemotherapy only. The three subsequent evaluations were at the sixth cycle of chemotherapy, and at six and at 12 months after starting treatment. Completion rates for these questionnaires declined from 90% for the first questionnaire to 83%, 83%, and 80% for the second, third, and fourth questionnaires respectively. Nevertheless, lower completion rates were noted in the IDS group compared to the chemotherapy only group, especially at the second assessment, 77% and 89%, respectively ($P < 0.001$).

The included trials are described in detail below and in the table of [Characteristics of included studies](#).

Excluded studies

After obtaining the full text, we excluded 18 studies for the following reasons:

- ten references reported on non-comparable controlled trials or non-randomised studies ([Kuhn 2001](#); [Recchia 2001](#); [Chan 2003](#); [Ikeba 2004](#); [Angioli 2006](#); ; [Fuso 2006](#); [Giannopoulos 2006](#); [Lee 2006](#); [Matulonis 2009](#); [Onda 2009](#));
- IDS was allowed in both arms of the trial in [Park-Simon 2006](#); [Vergote 2010](#);
- in [Dutta 2005](#) survival outcomes were not analysed;
- IDS was selectively performed in a subset of patients in [Solomon 1988](#);
- in [Evdokimova 1982](#), women with ascites were not randomly assigned to interventions;
- [Kumar 2009](#) allowed either histology or cytology for a pathologic diagnosis of ovarian cancer, and there had been no attempt to do PDS in the NAC arm;
- [Liu 2004](#) was considered ineligible because NAC was given for only one cycle via intra-arterial route before the IDS.
- [Polcher 2009](#) selected patients with ascites ≥ 500 cc, without PDS, to have two or three cycles of NAC prior to surgery.

For further details of all the excluded studies see the table [Characteristics of excluded studies](#).

Risk of bias in included studies

Two trials ([Redman 1994](#); [Van der Burg 1995](#)) were at moderate risk of bias: they satisfied three of the criteria that we used to assess risk of bias. [Rose 2004](#) was considered to be at high risk of bias as it satisfied only one of the criteria (see [Figure 1](#); [Figure 2](#)).

[Redman 1994](#) and [Van der Burg 1995](#) reported the method of generation of the sequence of random numbers used to allocate women to treatment arms. They also reported concealment of the allocation sequence from participants and healthcare professionals involved in the trial. [Rose 2004](#) reported neither the method of sequence generation nor concealment of allocation. None of the trials reported whether the outcome assessors were blinded. It was not clear whether all three trials reported all the outcomes that

they assessed, and it was unclear whether any other biases may have been present. At least 87% of the women who were enrolled were assessed at end point in the three trials. There were too few trials to support a funnel plot, so the possibility of reporting bias could not be explored.

Effects of interventions

IDS versus chemotherapy only

Survival

Overall survival (OS) (Analysis 1.1)

Meta-analysis of three trials ([Redman 1994](#); [Rose 2004](#); [Van der Burg 1995](#)), assessing 781 participants, found no statistically significant difference in the risk of death between IDS with chemotherapy and chemotherapy alone (hazard ratio (HR) = 0.80, 95% confidence interval (CI) 0.61 to 1.06). The percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) may represent substantial heterogeneity ($I^2 = 58\%$). Hence, we explored the sources of heterogeneity from the clinical factor of the expertise of the surgeon in the primary surgery, and subsequently performed subgroup meta-analysis for OS based on this factor.

The conclusions above were not robust to subgroup analyses examining women who received surgery from general surgeons (or had less extensive primary surgery) separately from gynaecologic oncologists. Meta-analysis of two trials ([Redman 1994](#); [Van der Burg 1995](#)) assessing 357 women who received surgery from a general surgeon found that IDS with chemotherapy was associated with a statistically significant decrease in the risk of death compared with chemotherapy alone (HR = 0.68, 95% CI 0.53 to 0.87, $I^2 = 0\%$).

[Rose 2004](#), assessing 424 participants, found no statistically significant difference in the risk of death between IDS with chemotherapy and chemotherapy alone (HR = 0.99, 95% CI 0.79 to 1.24. [Analysis 1.1](#)).

Progression-free survival (PFS) (Analysis 1.2)

Meta-analysis of two trials ([Van der Burg 1995](#); [Rose 2004](#)), assessing 781 participants, found no statistically significant difference in the risk of disease progression between IDS with chemotherapy and chemotherapy alone (HR = 0.88, 95% CI 0.57 to 1.33; [Analysis 1.2](#)). The percentage of the variability in effect estimates that is due to heterogeneity rather than chance may represent considerable heterogeneity ($I^2 = 83\%$).

Adverse events

Toxic reactions were the only adverse events which could be meta-analysed. They were reported in both treatment groups in [Redman 1994](#) and [Van der Burg 1995](#). It was not possible to meta-analyse other adverse events as they were not reported in sufficient detail for both treatment arms.

Toxic reactions to chemotherapy (Analysis 1.3)

Meta-analysis of two trials ([Redman 1994](#); [Van der Burg 1995](#)), assessing 357 participants, found no statistically significant difference in the risk of disease progression between IDS with chemotherapy and chemotherapy alone (HR = 1.19, 95% CI 0.53 to 2.66; [Analysis 1.3](#)). The percentage of the variability in effect estimates that is due to heterogeneity rather than to chance is insignificant ($I^2 = 0\%$).

The following adverse events were reported in [Rose 2004](#):

Peripheral neuropathy of grade 2 or higher (Analysis 1.4)

Women who received IDS with chemotherapy for treatment of advanced epithelial ovarian cancer had a significantly higher risk of high grade peripheral neuropathy than women who received chemotherapy alone (risk ratio (RR) = 0.62, 95% CI 0.43 to 0.91. [Analysis 1.4](#)).

Grade 3 or 4 gastrointestinal adverse events (Analysis 1.5)

There was no statistically significant difference in the risk of a high grade gastrointestinal adverse event between IDS with chemotherapy and chemotherapy alone (RR = 1.81, 95% CI 0.78 to 4.17. [Analysis 1.5](#)).

Grade 4 pulmonary adverse events (Analysis 1.6)

There was no statistically significant difference in the risk of a grade 4 pulmonary adverse event between IDS with chemotherapy and chemotherapy alone. There were only two observed events in the IDS group and no events in the chemotherapy only group. [Analysis 1.6](#).

Grade 4 cardiovascular adverse events (Analysis 1.7)

There was no statistically significant difference in the risk of a grade 4 cardiovascular adverse event between IDS with chemotherapy and chemotherapy alone (RR = 2.89, 95% CI 0.30 to 27.55. [Analysis 1.7](#)).

Quality of life (QoL)

Only [Rose 2004](#) evaluated QoL, which was subsequently reported by [Wenzel 2005](#). At six months after starting treatment, significantly more women who had only chemotherapy experienced persistent numbness or tingling than those who had IDS (54% versus 38%; $P = 0.01$). Otherwise, QoL was not significantly different in the two treatment groups at any time point.

DISCUSSION

Our systematic review includes three randomised controlled trials (RCTs), which evaluated 781 women out of 853 randomised, and a further RCT in abstract form which randomised 718 women, but it was unclear how many of these were evaluated. These four RCTs provide inconclusive evidence as to whether interval debulking surgery (IDS) improves or worsens the overall survival rate of patients. The random-effects model showed substantial heterogeneity between the results of the three trials. Similarly, meta-analysis of two RCTs which evaluated 702 women out of 767 randomised, provides inconclusive evidence about whether IDS improves or worsens progression-free survival; again, there was substantial heterogeneity between the trials.

There are potential reasons for the inconclusive evidence so far. Firstly, the small number of included studies, evaluating 781 women, may not have had adequate statistical power to detect a small effect. Furthermore, the studies had different characteristics, which may explain the heterogeneity in their results.

A major difference between these trials was the expertise and/or the level of effort given by the surgeons performing the primary debulking surgical procedures in the participating institutions in each study, which may partly explain the heterogeneity between trials. The majority of operations in the Gynecological Oncology Group (GOG) trial were performed by gynaecologic oncologists or fellowship-trained surgeons in various cancer centres ([Rose 2004](#)), while the surgical procedures in [Redman 1994](#) were performed mostly by general surgeons or gynaecologists in various hospitals. In the European Organisation for Research and Treatment of Cancer (EORTC) trial, where the expertise of the surgeon was not specified ([Van der Burg 1995](#)) but was subsequently revealed in other publications ([Kehoe 1995](#); [Van der Burg 2003](#)), the maximum effort to perform primary surgery was not attempted in all patients with different extents of debulking surgery. Since there is substantial evidence from many retrospective studies that the extent of optimal surgery affects the survival of patients with epithelial ovarian cancer ([Griffiths 1975](#); [Hoskin 1994](#); [Bristow 2002](#)), the maximum primary surgical efforts in the optimal surgical setting in the GOG trial might indicate that their primary surgery was sufficient and that subsequent surgical attempts would not further affect survival. Compared to [Redman 1994](#) and [Van der](#)

[Burg 1995](#), in which primary surgery was performed in suboptimal settings without gynaecologic oncologists ([Redman 1994](#)), without maximum effort (with less extensive primary debulking surgery) resulting in a high proportion of large residual tumours ([Kehoe 1995](#); [Van der Burg 1995](#); [Van der Burg 2003](#)), so the secondary surgery (IDS) after the tumours were down-sized by chemotherapy appeared worthwhile, although significant only in the EORTC trial. Our subgroup meta-analysis confirmed that IDS had benefits in this particular subgroup of women. Nevertheless, this should be interpreted with caution because our subgroup analysis was based on only two trials ([Redman 1994](#); [Van der Burg 1995](#)).

The second minor difference between the trials is the timing of randomisation. [Redman 1994](#) was the only trial which randomised participants into two groups (to have or not to have IDS) at the start of the trial, and only 67% of those in the IDS group actually underwent surgery, because the remainder had disease progression or died before IDS. The other two larger trials randomised only the patients who showed some response to induction chemotherapy ([Van der Burg 1995](#); [Rose 2004](#)); this resulted in a high percentage of the women (approximately 93% in both trials) who were randomised actually undergoing IDS. This difference may affect the results of each trial, based on an intention-to-treat analysis.

We explored the women's disease characteristics as another potential reason for different effects of IDS on survival outcomes: [Redman 1994](#) and [Rose 2004](#) did not show any advantage of IDS, while [Van der Burg 1995](#) showed significant survival improvement with IDS. [Redman 1994](#) evaluated only 79 of the total of 86 women included in the meta-analysis of OS and, therefore had limited weight in the results of the meta-analysis. The difference in outcomes from [Rose 2004](#) and [Van der Burg 1995](#) may be due to the different proportion of women who had a poor response to induction chemotherapy, and who generally had poorer prognoses than those who showed some response: approximately 52% of women in the GOG trial had residual diseases of more than 1 cm after induction chemotherapy ([Rose 2004](#)), compared to 44% in the EORTC trial ([Van der Burg 1995](#)). This might be interpreted as the GOG trial having a higher proportion of participants with more aggressive tumours who would not benefit from any treatment, even optimal IDS. However, this mechanism of tumour aggression and prognosis may not solely explain the women's ultimate outcome, because the women in the EORTC trial who had a tumour greater than 1 cm after induction chemotherapy but which was reduced to less than 1 cm had better survival rates than any other group of women in the trial. This might suggest that IDS may play some role in survival improvement.

To emphasize the importance of the sensitivity of response to chemotherapy before IDS, we would draw attention to the findings from the GOG and EORTC trials which showed that the women whose tumour masses were reduced by chemotherapy to less than 1 cm before the IDS ([Van der Burg 1995](#); [Rose 2004](#)) had better

survival than the other groups. This response to chemotherapy might be used as a selection criterion for the women who are most likely to gain survival benefit from an IDS procedure.

As we have mentioned in the results, meta-analysis of adverse events was not possible due to different formats of presentation of data in each RCT. The only obvious advantage appears to be fewer neurologic complications in the IDS group than in the chemotherapy only group in the GOG trial (Rose 2004). However, this adverse effect may be related to a particular drug and might not be experienced in other settings using different chemotherapeutic regimens.

For the quality of life (QoL) comparison, which was only assessed by the GOG trial (Wenzel 2005), women in the chemotherapy only arm had a higher rate of neurotoxicity than did those in the IDS arm at one of the four time points at which they were assessed, despite a similar total dose of chemotherapy exposures. The authors ascribe this finding to intermission from chemotherapy exposure allowing a certain degree of recovery, but it may be a chance finding, as 48 tests of possible differences in QoL were made. Although other aspects of QoL were similar in the two groups of women at every time point, definitive conclusions cannot be drawn, because a significantly lower proportion of women in the IDS group completed the QoL questionnaires in the second assessment compared to those in the chemotherapy only group, and it is possible that this lower questionnaire completion rate may be associated with QoL.

AUTHORS' CONCLUSIONS

Implications for practice

The heterogeneity of the results in our review precludes any definitive guidance or recommendations for clinical practice. Without strong evidence to support the superiority of interval debulking surgery (IDS) in combination with chemotherapy over conventional primary surgery and chemotherapy, a clinician may remain unconvinced of the benefit of IDS instead of aggressive primary surgery for a woman with advanced ovarian cancer. The choice of extensive primary surgery or upfront chemotherapy followed by IDS must be individualized to each patient. Since we found a benefit of IDS in the subgroup of women whose primary surgery

had not been performed under optimal conditions by the oncologic surgeons or without maximum surgical effort, we suggest that IDS may improve patient survival in this setting. However, if the primary surgery has already been performed by the oncologic surgeons or with maximal surgical effort, IDS may not yield any further benefit for survival. Nevertheless, in a situation when there is evidence that primary surgery would be impossible or that morbidity from surgery would outweigh the benefit, induction chemotherapy followed by IDS may have a role to play.

Implications for research

The theoretical benefit of IDS needs further well-designed randomised controlled trials to generate evidence which may resolve the equivocal findings of this review.

These studies should focus on a comparison of current conventional primary surgery with adjuvant chemotherapy versus neoadjuvant chemotherapy (without any attempt to remove the bulk of tumours except a biopsy for histologic diagnosis) followed by IDS, and then by further chemotherapy.

The level and expertise of the surgeon or the effort in performing the primary surgery should be standardised as far as possible, in order to obtain the best surgical outcome. The particular subgroup of women with their specific disease characteristics should be a set criterion for IDS, e.g. patients with only small tumours after induction or neoadjuvant chemotherapy.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Redman 1994

Methods	Study duration: April 1986 to February 1990. Type of trial: Multicentre RCT, intention-to-treat analysis.	
Participants	Stage II-IV (except unresectable stage IV diseases). Performance status ECOG: at least 2. Histology proven, with exclusion of borderline tumour. Primary surgery must be performed through an appropriate incision/ a maximal attempt to remove tumours. Residual disease status > 2 cm. No evidence of progressive disease, extraperitoneal tumour > 1 cm, or had excessive delay after induction chemotherapy and before randomisation Baseline characteristics (N = 86): 24 women aged <50, 25 between 50 - 60, and 30> 60 years. 50 women had performance status 0 or 1, 20 status 2 and 9 women had status 3 or 4. 6 women were diagnosed with FIGO stage IIB, 62 stage III and 11 had stage IV disease. 39 women had residual disease between 2 - 5 cm, 29 between 5 - 10 cm and 11 >10 cm. Histology type was as follows: Serous 32, mucinous 6, endometrioid 13, clear cell 4, undifferentiated 6 and unspecified 20. Histology differentiation was as follows: Poor 37, moderate 27, well 6 and unspecified 9	
Interventions	Intervention: IDS: after 1 - 4 cycles of induction chemotherapy consisting of IV cisplatin 75 mg/m ² + cyclophosphamide 750 mg/m ² or cisplatin 75 mg/m ² + doxorubicin 50 mg/m ² + bleomycin 50 mg/m ² followed by escalated dose of cyclophosphamide (0.5 g/m ² -2.5 g/m ²) up to 5 cycles. Chemotherapy cycles were repeated every 3 weeks. Control: No IDS: the same regimen of chemotherapy was given in a row every 3 weeks	
Outcomes	Overall survival (OS). Perioperative complications: primary haemorrhage, blood transfusion, deep vein thrombosis, intestinal fistula, postoperative febrile morbidity, postoperative ileus	
Notes	Randomised at entry (within 4 weeks after primary surgery). Number ineligible: 7 (primary surgery was not suboptimal). Only 9% of primary surgeons were gynaecologic oncologists. IDS performed by the primary surgeon. Response evaluation by physical examination, imaging studies (CA125 not used). OS was measured from the date of entry. Rate of complications was described only in the IDS group.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Redman 1994 (Continued)

Random sequence generation (selection bias)	Low risk	“Randomisation sheets were produced by the random permuted blocks methods utilising the NAG Fortran Library subroutine to generate random numbers”
Allocation concealment (selection bias)	Low risk	“These preprinted sheets were kept at the trial’s office and medical personnel were given no access to them”
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	N analysed: 79/86 (92%)
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Rose 2004

Methods	Study duration: June 1994 to January 2001. Type of trial: Multicentre RCT, intention-to-treat basis.
Participants	Stage III-IV (malignant pleural effusion or a resected anterior abdominal wall tumour) (exclusion of stage IV after March 1996 after EORTC reported a greater benefit from secondary surgery after the exclusion of such patients from the analyses). Age < 75 years Performance status ACOG: 0 - 2 with life expectancy of at least 8 weeks. Primary surgery performed within 6 weeks before chemotherapy. Primary surgery aimed to remove as much as possible. Histology proven, with central pathologic review. Residual disease status > 1 cm. Had no delay of chemotherapy treatment > 2 weeks. Baseline characteristics (N = 448): Median age 58.1 (range: 25.4 - 81.6 years) in the IDS group and 57 (range: 27-81.6 years) in the no IDS group. 166 women had GOG performance status 0, 227 had status 1 and 31 women had status 2. 400 women were diagnosed with FIGO stage III and 24 had stage IV disease. 297 women had measurable disease. 53 women had residual disease between 1 - 2 cm, 183 between 2.1 - 5 cm, 150 between 5.1 - 10 cm and 38 >10 cm. Histology type was as follows: Serous 324, mucinous 3, endometrioid 28, clear cell 7, mixed epithelial 37, adenocarcinoma (unspecified) 12 and undifferentiated or other 13.

	Histology grade was as follows: 1: 40, 2: 167, 3 or clear cell: 217
Interventions	Intervention: IDS: after 3 cycles of chemotherapy consisting of IV paclitaxel 135 mg/m² + cisplatin 75 mg/m² every 3 weeks. Three more cycles of the same chemotherapy regimen were given after IDS. No IDS: the same regimen of chemotherapy was given in a row every 3 weeks for 6 cycles
Outcomes	Overall survival. Progression-free survival. Adverse effects: peripheral neuropathy, haematologic effects, gastrointestinal events, pulmonary events, cardiovascular events, and cause of death. Quality of life.
Notes	Randomised after 3 cycles of chemotherapy. Number ineligible: 24 Majority of surgeons for primary and secondary surgery (IDS) were gynaecologic oncologists. Response evaluation by physical examination, imaging studies, and CA125. Consolidation chemotherapy was allowed. Overall and progression-free survival were measured from the date of randomisation and also from the date of enrolment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	N analysed: 424/448 (95%)
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Van der Burg 1995

Methods	Study duration: March 1987 to May 1993. Type of trial: Multicentre RCT, intention-to-treat analysis.	
Participants	Stage IIB-IV. Age of participants < 75 years. Performance status WHO: 0-2. Primary surgery performed within 6 weeks before induction chemotherapy. Histology proven, with central pathologic review. Residual disease status > 1 cm. Have some response or stable disease after induction chemotherapy without evidences of progressive diseases or had contraindication to surgery. Baseline characteristics (N = 319): Median age was 59 years in both groups (range: 32 - 74). 68 women had performance status 0, 99 status 1, and 33 status 2. 10 women were diagnosed with FIGO stage IIB, 146 stage III and 44 had stage IV disease. 10 women had residual disease between 1 - 2 cm, 45 between 2 - 5 cm, 44 between 5 - 10cm, 60 >10 cm and 41 unknown but > 2 cm. Histology type was as follows: Serous 115, mucinous 12, endometrioid 17, clear cell 5, and unclassified 51. Histology grade was as follows: 1: 17, 2: 59, 3: 105 and unknown: 9	
Interventions	Intervention: IDS: after 3 cycles of induction chemotherapy composing of IV cyclophosphamide 750 mg/m ² + IV cisplatin 75 mg/m ² every 3 weeks. Three more cycles of the same chemotherapy regimen were given after IDS. No IDS: the same regimen of chemotherapy was given in a row every 3 weeks for 6 cycles	
Outcomes	Overall survival. Progression-free survival. Perioperative complications: bowel injury, urinary bladder injury, blood loss, postoperative fever, ileus, urinary tract infection, wound infection, deep vein thrombosis, lung embolism. Clinical response rate after 6 cycles of chemotherapy.	
Notes	Randomised after 3 cycles of induction chemotherapy at Central EORTC data centre, after stratification with a minimization technique to account for institution, performance status, and clinical response. Number ineligible: 4 Response evaluation by WHO response criteria. Consolidation chemotherapy after 6 cycles was allowed based on institutions policy. Survivals were measured from the first date of chemotherapy (after enrolment). Rate of complications was detailed only in the IDS group	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	“Randomization was done ... after stratification with a minimization technique to account for institution, performance status, and clinical response”
Allocation concealment (selection bias)	Low risk	“Randomization was done centrally at the EORTC Data Center”
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	N analysed: 278/319 (87%)
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Angioli 2006	This study was evaluated as a non-comparable controlled clinical trial. NAC followed by IDS was selectively given to the women based on initial laparoscopic findings of inoperability
Chan 2003	This study was evaluated as an uncontrolled clinical trial. NAC was given to the women without a control group. The women were selected by their inoperability based on CT scan without primary operation being attempted. Either histology or only cytology was allowed for a pathologic diagnosis of ovarian cancer
Dutta 2005	This was an RCT of ovarian cancer patients to have either 3 cycles of NAC followed by IDS and further chemotherapy versus 6 cycles of NAC before surgery. Main objective was to study proapoptotic and antiapoptotic proteins in ovarian cancer tissue without survival outcome evaluation
Evdokimova 1982	This was an RCT comparing survival of women with ovarian carcinoma who had NAC/IDS versus conventional treatment of surgery then chemotherapy. However, those without ascites were selected to have primary surgery followed by chemotherapy while those with ascites had either NAC/IDS or conventional treatment
Fuso 2006	This uncontrolled prospective study was to assess the feasibility of triple chemotherapy composed of gemcitabine, carboplatin, and paclitaxel as first-line drugs in advanced ovarian cancer. The women were selectively assigned to have two different types of treatment. After laparoscopic biopsy in all participants, those who were judged to be operable underwent primary surgery followed by chemotherapy, while the inoperable women were given NAC followed by IDS. However, few who had primary surgery also had IDS

(Continued)

Giannopoulos 2006	This study was evaluated as a non-comparable controlled clinical trial. NAC and IDS was selectively given to the women who were deemed to be inoperable based on CT scan and initial laparoscopic findings. Either histology or cytology was allowed for a pathologic diagnosis of ovarian cancer
Ikeba 2004	This study was evaluated as an uncontrolled clinical trial. NAC was given to all, without a control group
Kuhn 2001	This study was evaluated as a non-comparable controlled clinical trial. NAC was selectively given to women in poor general health for primary surgery. The control group consisted of those who did not agree to the study protocol or were ineligible for treatment for psychological reasons
Kumar 2009	This RCT allowed either histologic or cytologic diagnosis. NAC was given to the study arm without an attempt to perform a PDS
Lee 2006	This study was evaluated as a non-comparable controlled clinical trial. NAC was selectively given to those who agreed to undergo the NAC treatment protocol. NAC cycles ranged from three to six. Some women had secondary surgery which was not in an interval setting
Liu 2004	This RCT was considered as ineligible because NAC was given only for one cycle via intra-arterial route before the IDS
Madhuri 2014	RCT comparing the efficacy of neutral argon plasma to standard surgery during PDS or IDS
Matulonis 2009	This prospective study was a non-randomised study. The women aged 75 - 86 years with stage II - IV disease to have PDS followed by adjuvant chemotherapy or to have NAC if they had poor performance status or inoperable metastatic disease. All five women who had NAC were not able to undergo surgery
Onda 2009	This was a prospective single arm study to evaluate the role of diagnostic laparoscopy in those with a diagnosis of Mullerian carcinoma
Onda 2014	This RCT compared PDS or NAC then IDS followed more cycles of chemotherapy. IDS was performed in both arms: 31.3% in the PDS arm and 86.8% in the IDS arm
Park-Simon 2006	This RCT compared survivals of ovarian cancer patients who had ascites > 500 cc who were given NAC for either two versus three cycles, but followed by IDS in both arms
Polcher 2009	This RCT randomised women with ascites > 500 cc to have two or three cycles of NAC without an attempt to do PDS
Recchia 2001	This study was evaluated as an uncontrolled clinical trial. NAC was given to all without a control group. Either histology or only cytology was allowed for a pathologic diagnosis of ovarian cancer
Solomon 1988	This study was presented in conjunction with the prior RCT comparing combination versus sequential chlorambucil and cisplatin. IDS in this study was selectively performed only in the subset of women who had not been debulked at primary surgery. Second-look surgery or surgical re-exploration were also performed on those with clinical complete remission or on those with complications requiring surgery, respectively
Tiersten 2009	This was a prospective single arm study when the women must have had no aggressive PDS before receiving intraperitoneal chemotherapy followed by surgery

(Continued)

Vergote 2010	This RCT compared the role of PDS followed by adjuvant chemotherapy in the control arm with NAC before IDS followed by additional chemotherapy in the study arm. However, IDS was also allowed in the PDS arm too, at the discretion of the physician. Furthermore, either histologic or cytologic diagnosis (with tumour marker and imaging criteria to exclude cancers of other non-Mullerian origins) was allowed.

IDS: interval debulking surgery
NAC: neoadjuvant chemotherapy
RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. IDS vs chemotherapy only

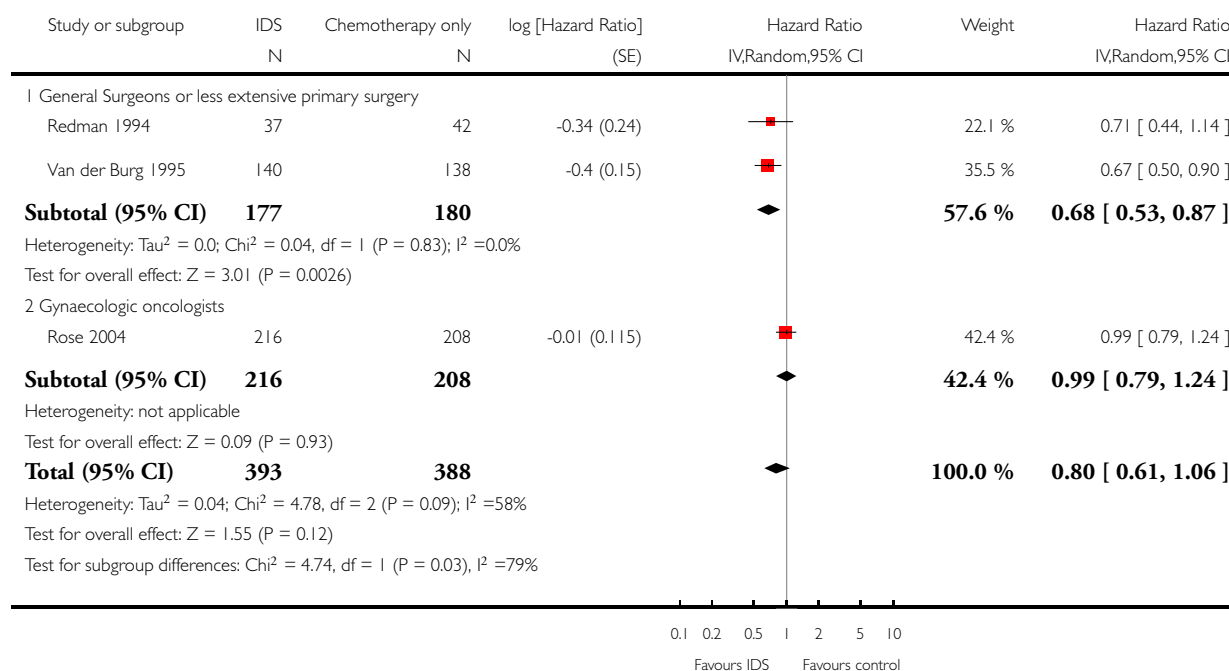
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	3	781	Hazard Ratio (Random, 95% CI)	0.80 [0.61, 1.06]
1.1 General Surgeons or less extensive primary surgery	2	357	Hazard Ratio (Random, 95% CI)	0.68 [0.53, 0.87]
1.2 Gynaecologic oncologists	1	424	Hazard Ratio (Random, 95% CI)	0.99 [0.79, 1.24]
2 Progression-free survival	2	702	Hazard Ratio (Random, 95% CI)	0.88 [0.57, 1.33]
3 Toxic reactions to chemotherapy	2	357	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.53, 2.66]
4 Peripheral neuropathy of grade 2 or higher	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
5 Grade 3 or 4 gastrointestinal adverse events	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
6 Grade 4 pulmonary adverse events	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
7 Grade 4 cardiovascular adverse events	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 IDS vs chemotherapy only, Outcome 1 Overall survival.

Review: Interval debulking surgery for advanced epithelial ovarian cancer

Comparison: 1 IDS vs chemotherapy only

Outcome: 1 Overall survival

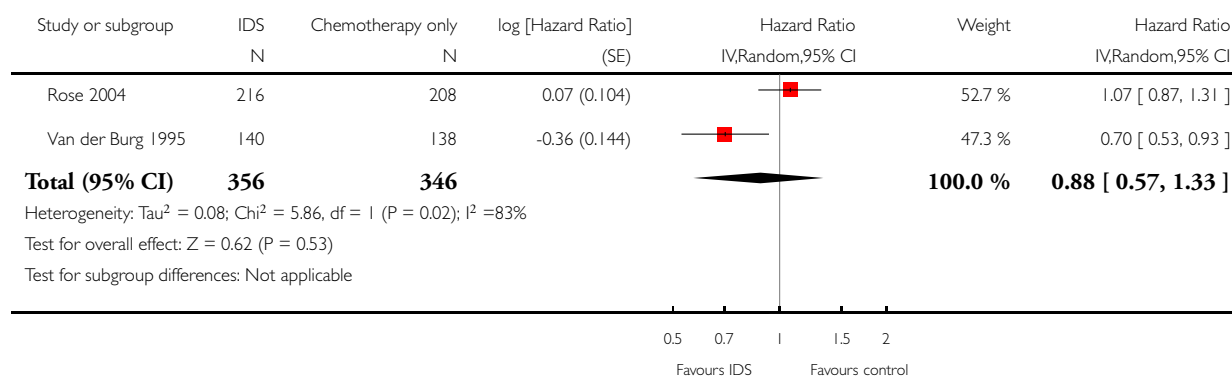


Analysis 1.2. Comparison 1 IDS vs chemotherapy only, Outcome 2 Progression-free survival.

Review: Interval debulking surgery for advanced epithelial ovarian cancer

Comparison: 1 IDS vs chemotherapy only

Outcome: 2 Progression-free survival

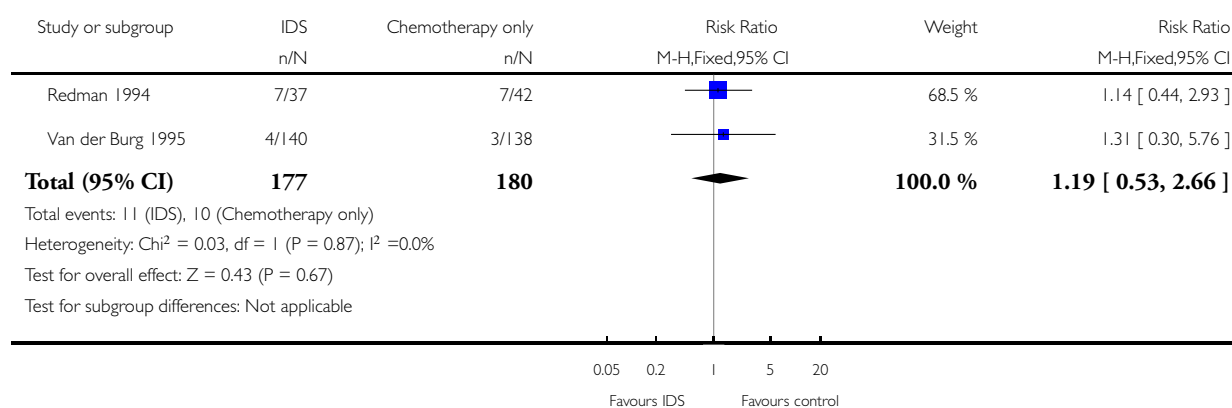


Analysis 1.3. Comparison 1 IDS vs chemotherapy only, Outcome 3 Toxic reactions to chemotherapy.

Review: Interval debulking surgery for advanced epithelial ovarian cancer

Comparison: 1 IDS vs chemotherapy only

Outcome: 3 Toxic reactions to chemotherapy

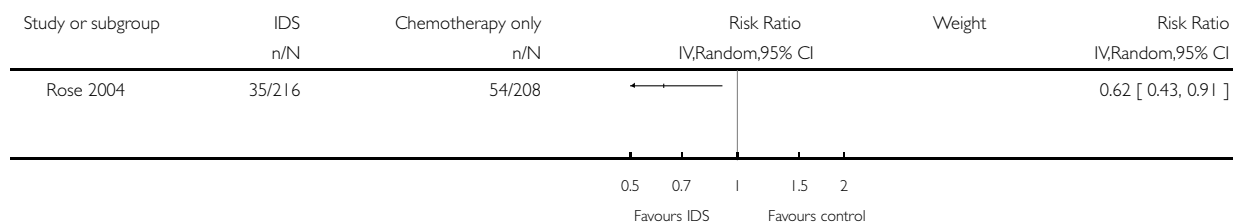


Analysis 1.4. Comparison 1 IDS vs chemotherapy only, Outcome 4 Peripheral neuropathy of grade 2 or higher.

Review: Interval debulking surgery for advanced epithelial ovarian cancer

Comparison: 1 IDS vs chemotherapy only

Outcome: 4 Peripheral neuropathy of grade 2 or higher

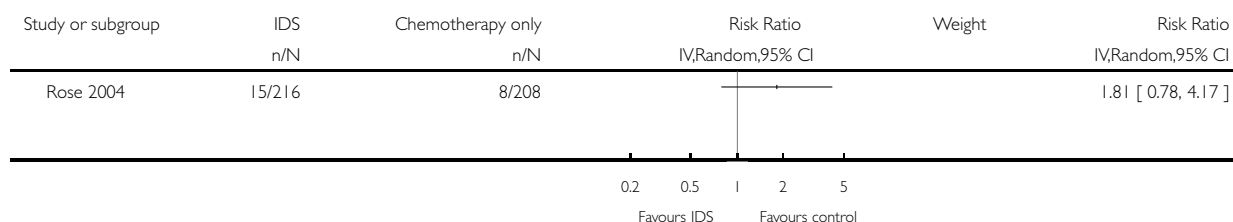


Analysis 1.5. Comparison 1 IDS vs chemotherapy only, Outcome 5 Grade 3 or 4 gastrointestinal adverse events.

Review: Interval debulking surgery for advanced epithelial ovarian cancer

Comparison: 1 IDS vs chemotherapy only

Outcome: 5 Grade 3 or 4 gastrointestinal adverse events

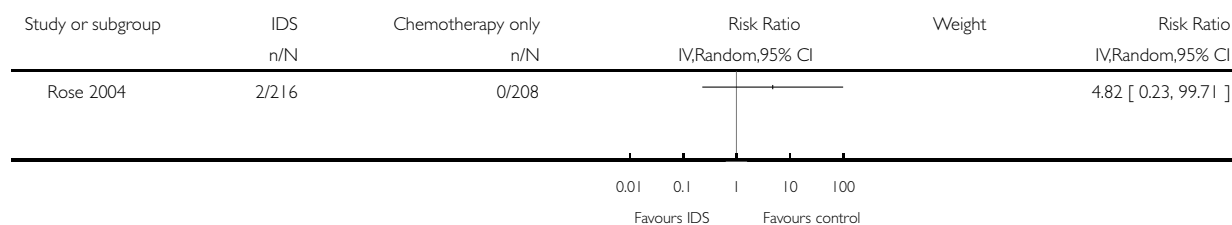


Analysis 1.6. Comparison 1 IDS vs chemotherapy only, Outcome 6 Grade 4 pulmonary adverse events.

Review: Interval debulking surgery for advanced epithelial ovarian cancer

Comparison: 1 IDS vs chemotherapy only

Outcome: 6 Grade 4 pulmonary adverse events

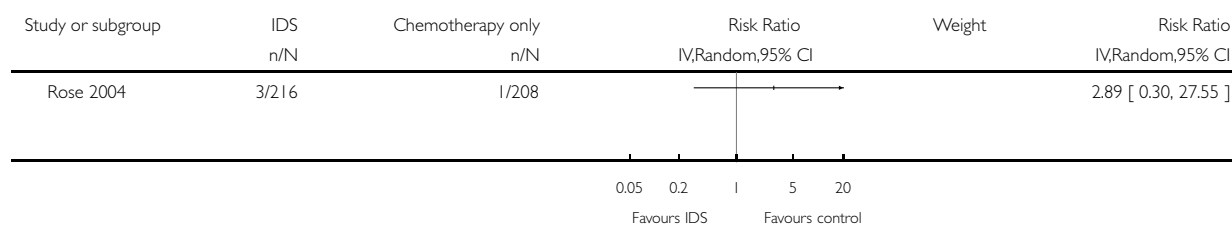


Analysis 1.7. Comparison 1 IDS vs chemotherapy only, Outcome 7 Grade 4 cardiovascular adverse events.

Review: Interval debulking surgery for advanced epithelial ovarian cancer

Comparison: 1 IDS vs chemotherapy only

Outcome: 7 Grade 4 cardiovascular adverse events



APPENDICES

Appendix 1. MEDLINE Ovid

- 1 exp Ovarian Neoplasms/
 - 2 (ovar* adj5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)).mp.
 - 3 1 or 2
 - 4 exp Surgical Procedures, Operative/
 - 5 surg*.mp.
 - 6 surgery.fs.
 - 7 4 or 5 or 6
 - 8 (interval or debulk* or cytoreduc* or secondary).mp.
 - 9 3 and 7 and 8
 - 10 randomized controlled trial.pt.
 - 11 controlled clinical trial.pt.
 - 12 randomized.ab.
 - 13 randomly.ab.
 - 14 trial.ab.
 - 15 groups.ab.
 - 16 10 or 11 or 12 or 13 or 14 or 15
 - 17 9 and 16
- key: mp = title, original title, abstract, name of substance word, subject heading word
fs = floating subheading
pt = publication type
ab = abstract
sh = subject heading

Appendix 2. EMBASE

- 1 exp ovary tumor/
 - 2 (ovar* adj5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)).mp.
 - 3 1 or 2
 - 4 exp surgery/
 - 5 surg*.mp.
 - 6 su.fs.
 - 7 4 or 5 or 6
 - 8 (interval or debulk* or cytoreduc* or secondary).mp.
 - 9 7 and 8
 - 10 exp cytoreductive surgery/
 - 11 9 or 10
 - 12 3 and 11
 - 13 exp controlled clinical trial/
 - 14 randomized.ab.
 - 15 randomly.ab.
 - 16 trial.ab.
 - 17 groups.ab.
 - 18 13 or 14 or 15 or 16 or 17
 - 19 12 and 18
- key: mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name
fs = floating subheading
ab = abstract

Appendix 3. CENTRAL

- #1 MeSH descriptor Ovarian Neoplasms explode all trees
- #2 ovar* near/5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)
- #3 (#1 OR #2)
- #4 MeSH descriptor Surgical Procedures, Operative explode all trees
- #5 surg*
- #6 Any MeSH descriptor with qualifier: SU
- #7 (#4 OR #5 OR #6)
- #8 interval or debulk* or cytoreduc* or secondary
- #9 (#3 AND #7 AND #8)

WHAT'S NEW

Last assessed as up-to-date: 1 June 2015.

Date	Event	Description
7 January 2016	Amended	Additional reference amended.
4 January 2016	New search has been performed	Searches updated in June 2015.
4 January 2016	New citation required but conclusions have not changed	We did not identified any new studies for inclusion.
4 January 2016	Amended	CRG funding acknowledgment added.

HISTORY

Protocol first published: Issue 2, 2006

Review first published: Issue 4, 2008

Date	Event	Description
5 March 2013	New search has been performed	Two RCTs were identified and subsequently excluded.
5 March 2013	New citation required but conclusions have not changed	The search was updated to June 2012.
19 August 2010	Amended	Searches re-run in July 2009. Seventeen possible relevant articles were identified. Only two RCTs were found; one RCT of a Japanese study and the EORTC 55971 trial. However, the Japanese study referred to a study that was excluded in our primary review and EORTC 55971 trial allowed IDS in both arms at discretion of physician

(Continued)

10 February 2009	Feedback has been incorporated	Feedback regarding new trial incorporated.
10 November 2008	New citation required but conclusions have not changed	Errors in reporting HR and RR corrected. Explanation regarding surgical expertise included

CONTRIBUTIONS OF AUTHORS

ST and SM: protocol development, searching for and determining the relevance of trials for the review, assessing their methodological quality, extracting data, and review development. ML: protocol development, data analysis, and review development. PL: protocol development, providing methodological advice throughout the review, arbitration over any disagreements, advising on the content and presentation of the review. AB: methodological and statistical support.

DECLARATIONS OF INTEREST

There is no known conflict of interest among the authors of this review.

SOURCES OF SUPPORT

Internal sources

- Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Thailand.
- Faculty of Medicine, Khon Kaen University, Thailand.
- Faculty of Public Health, Khon Kaen University, Thailand.

External sources

- Thailand Research Fund (Outstanding Research Professor Award), Thailand.
- Cochrane Thailand, Thailand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None of the trials reported continuous outcomes such as quality of life (QoL), or had multiple treatment groups. We had originally specified the following in various sections of the protocol.

- For continuous outcomes (e.g. QoL measures), we will extract the final value and standard deviation of the outcome of interest and the number of patients assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference (if trials measured outcomes on the same scale) or standardised mean differences (if trials measured outcomes on different scales) between treatment arms and its standard error.
- For continuous outcomes, we will use the mean difference between treatment arms.
- For continuous outcomes, the mean differences between the treatment arms at the end of follow-up will be pooled if all trials measured the outcome on the same scale, otherwise standardised mean differences will be pooled.
- If any trials have multiple treatment groups, the 'shared' comparison group will be divided into the number of treatment groups and comparisons between each treatment group and the split comparison group will be treated as independent comparisons.

- Where possible, indirect comparisons, using the methods of [Bucher 1997](#) will be used to compare competing interventions that have not been compared directly with each other.

We had planned to compute funnel plots, but this was not possible due to an insufficient number of included trials in the review. The protocol stated the following:

Funnel plots corresponding to meta-analysis of the primary outcome will be examined for evidence of small study effects. If such evidence exists, publication bias and other possible explanations will be considered. If funnel plots suggest that treatment effects may not be sampled from a symmetric distribution, as assumed by the random-effects model, sensitivity analyses will be performed using fixed-effect models.

We planned to perform sensitivity analyses to evaluate whether the pooled effect sizes were robust across components of methodological quality. However, only one trial reported adequate concealment of allocation ([Redman 1994](#)) and other components of quality were similar across studies, so these sensitivity analyses were not performed.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [*therapeutic use]; Chemotherapy, Adjuvant [mortality]; Combined Modality Therapy [methods]; Induction Chemotherapy [mortality]; Neoadjuvant Therapy [methods; mortality]; Ovarian Neoplasms [*drug therapy; mortality; pathology; *surgery]; Quality of Life; Randomized Controlled Trials as Topic; Survival Rate; Tumor Burden [drug effects]

MeSH check words

Female; Humans



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Pharmacological interventions for generalised itching (not caused by systemic disease or skin lesions) in pregnancy (Review)

Rungsiprakarn P, Laopaiboon M, Sangkomkarnhang US, Lumbiganon P

Rungsiprakarn P, Laopaiboon M, Sangkomkarnhang US, Lumbiganon P.

Pharmacological interventions for generalised itching (not caused by systemic disease or skin lesions) in pregnancy.

Cochrane Database of Systematic Reviews 2016, Issue 2. Art. No.: CD011351.

DOI: 10.1002/14651858.CD011351.pub2.

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	2
OBJECTIVES	4
METHODS	5
RESULTS	6
Figure 1.	7
DISCUSSION	8
AUTHORS' CONCLUSIONS	8
ACKNOWLEDGEMENTS	8
REFERENCES	9
CHARACTERISTICS OF STUDIES	11
DATA AND ANALYSES	13
APPENDICES	13
CONTRIBUTIONS OF AUTHORS	16
DECLARATIONS OF INTEREST	17
SOURCES OF SUPPORT	17
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	17
INDEX TERMS	18

Pharmacological interventions for generalised itching (not caused by systemic disease or skin lesions) in pregnancy

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Editorial group: Cochrane Pregnancy and Childbirth Group.

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ABSTRACT

Background

Generalised itching is one of the most common dermatological symptoms in pregnant women. Having itchy skin during pregnancy may be very frustrating and can lead to poor sleep, exhaustion and impaired quality of life. There is a need for a systematic review to evaluate the effectiveness and safety of pharmacological interventions for treating itching in pregnancy.

Objectives

To assess the effectiveness and safety of pharmacological interventions for treating generalised itching (not caused by systemic diseases or skin lesions) in pregnancy.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (28 January 2016) and the reference list of the one identified study.

Selection criteria

All published, unpublished and ongoing randomised controlled trials (RCTs) evaluating interventions for itching in pregnancy.

Quasi-RCTs, cluster-RCTs, RCTs using a cross-over design, and studies reported in abstract form (without full text) were not eligible for inclusion.

Data collection and analysis

Two review authors independently assessed the one trial report that was identified from the search strategy and this was subsequently excluded.

Main results

There are no included studies as we did not identify any relevant trials.

Authors' conclusions

Generalised itching (not caused by systemic disease or skin lesions) is quite a common symptom in pregnancy. However, there is no evidence from randomised controlled trials to guide practice in terms of the effectiveness and safety of pharmacological interventions for treating this condition.

Well-designed randomised controlled trials are needed in order to evaluate the effectiveness of topical and systemic pharmacological interventions as well as any adverse effects of the interventions. Such studies should consider important outcomes such as relief of itching, women's satisfaction, sleep disturbance, and adverse effects.

PLAIN LANGUAGE SUMMARY

Medications for generalised itching (not caused by a disease affecting the whole body or changes in the skin (lesions) during pregnancy

Itching, or an unpleasant sensation that provokes a desire to scratch, is one of the most common skin problems in pregnant women. It can be caused by skin diseases, diseases affecting the whole body, or simply by having dry skin, known as generalised itching. The growing uterus also stretches the skin around the belly and the skin containing oil glands which keep it moist are not able to meet the moisture requirement, leading to dry skin. For the pregnant woman, having itchy skin can add anxiety, frustration and lead to poor sleep and exhaustion. She may also cause skin damage from scratching.

We searched the medical literature for trials (28 January 2016) to determine the effectiveness of medications and any adverse effects of the medications used for the treatment of itching. Unfortunately, we found no evidence from randomised controlled trials to assess whether medications applied directly to the skin (topically) or taken systemically for generalised itching in pregnancy are effective or safe.

High-quality randomised controlled trials assessing medications for generalised itching (not caused by a disease affecting the whole body or changes in the skin (lesions) in pregnant women are needed. Such studies should consider important outcomes such as relief of itching, women's satisfaction, sleep disturbance and adverse effects of the interventions.

BACKGROUND

Description of the condition

Itching is one of the most common dermatological symptoms in pregnant women (Schroeder 2000). It can be defined as a poorly localised, unpleasant, irritating cutaneous sensation evoking the desire to scratch (Weisshaar 2005). Itching occurs in 17% to 18% of all pregnant women (Kroumpouzos 2002; Weisshaar 2009). The aetiologies of itching in pregnancy range from specific dermatoses (skin disorders) of pregnancy to various dermatological conditions such as atopic dermatitis, urticaria, infections, infestations, or they can be drug-induced. In addition, systemic diseases such as renal insufficiency, Hodgkin's lymphoma, polycythaemia vera, and many other conditions can also manifest with itching (Kar 2012; Krajnik 2001). Pregnancy-related dermatoses include pemphigoid (herpes) gestationis (pregnancy-associated autoimmune

skin disease), polymorphic eruption of pregnancy (pruritic urticarial papules and plaques of pregnancy), intrahepatic cholestasis of pregnancy, and atopic eruption of pregnancy (Ambros-Rudolph 2011; Rimoin 2013). Generalised itching is a term often used when primary skin lesions are absent. Most women with generalised itching do not have systemic disease (Herndon 1975), and xerosis (dry skin) is the most common cause of itching without skin lesions (Millikan 1996). In pregnancy, physiologic changes may result in itching, for instance, the expanding uterus stretches the skin around the belly, and the oil glands which keep the skin moist are unable to meet the moisture requirement, leading to dry skin. This condition causes significant itching and may be worsened by environmental factors, such as cold air, low humidity, or central heating (Tivoli 2009). Furthermore, itching can be stimulated in the skin directly by mechanical and thermal triggers or indirectly through chemical mediators (Stander 2003). Histamine is the major substance affecting itching as well as sero-

tonin, prostaglandins, epinephrine, acetylcholine, proteases, neuropeptides (substance P), opioids, growth factors, and cytokines (Charlesworth 2002; Hercogova 2005). Having itchy skin during pregnancy can add anxiety to an otherwise already stressful time for many women. Severe itching during pregnancy, although benign, may be very frustrating and can lead to poor sleep, exhaustion and impaired quality of life (Yosipovitch 2003). Itching usually leads to secondary lesions such as redness, erosions, and excoriations (Weisshaar 2005). Evaluating itching in pregnancy is imperative to determine whether the itching is related to a primary dermatological or systemic disease. The clinical approach to a pregnant women with itching includes history-taking, as well as thorough physical and laboratory investigations.

This topic of this review is generalised itching in pregnant women who do not have systemic disease or skin lesions (including atopic rashes). We did not consider studies of pregnant women with intrahepatic cholestasis (as this is covered by another Cochrane review (Gurung 2013)), pregnancy-related dermatoses and generalised pruritus (itching) with systemic disease.

Description of the intervention

In this review, we considered pharmacological interventions including topical and systemic drugs given specifically for itching in pregnancy. Topical agents include cooling agents, topical anaesthetics agents, topical steroid, and capsaicin cream. Systemic agents include antihistamine, aspirin, steroid, opioid antagonists, and antidepressants. In addition to using antipruritic medications, general therapeutic measures are also important when dealing with itching during pregnancy. Topical agents are usually the first-choice regimen along with general measures (Hercogova 2005), including the use of moisturisers, non-alkaline detergents, lukewarm baths, and cotton-made clothing. Moisturisers maintain the integrity of the epidermal barrier and promote its protective function against dehydration and irritants that may precipitate itching (Elias 2002; Twycross 2003). In addition, moisturisers seal in moisture and are recommended to be applied instantly after bathing on a daily basis to prevent transepidermal water loss (Simpson 2010). Pregnant women with generalised itching are advised to avoid wool and synthetic materials. Other approaches such as cold baths and sugar scrub cream is not covered in this review as it is restricted to pharmacological interventions.

Pharmacological intervention

Topical drugs

1. Cooling agents not only relieve itching, but also trigger dry skin with long-term use, which might cause recurrence of itching (Weisshaar 2005). They are commonly applied one to three

times a day (Twycross 2003). Calamine lotion and menthol are considered to be safe in pregnancy (Mehta 2014).

2. Topical anaesthetic agents are seldom used as they are associated with an increased risk of allergic sensitisation (Lynde 2008).

3. Topical steroids are available in different bases (e.g. solution, lotion, cream or ointment). The potency ranges from low to high or ultra-potent. The medium to ultra-potent topical steroids are applied for short courses (lasting one to three weeks), daily to twice daily, however with prolonged use close clinical monitoring may be required. Ultra-potent topical steroids, such as betamethasone dipropionate, may be useful to interrupt the itch-scratch cycle. Local side effects include atrophy, striae, pigmentation, acne, petechiae, telangiectasia and the potential risk from systemic absorption includes hypothalamus-pituitary axis suppression (Elmariah 2011).

4. Capsaicin (isolated from pepper) 0.025% to 0.1% cream is commonly applied four to six times daily (Metz 2011). The apparent side effect of local irritation (Lynde 2008) can be reduced by applying EMLA cream (eutectic mixture of local anaesthetics; lidocaine and prilocaine) prior to capsaicin application (Yosipovitch 1999). Importantly, the recommendation is that topical capsaicin is not to be used in pregnancy because of reported neurotoxic effects in animal studies (Weisshaar 2005).

Systemic drugs

1. Antihistamine: the first generation antihistamines are no longer recommended (Bousquet 2012). The side effects of second generation antihistamines, such as loratadine, fexofenadine, and cetirizine, include photosensitivity, tachycardia, and prolongation of the Q-T interval (Kar 2012). The United States Federal Drug Administration (FDA) considers loratadine as a category B drug, that is, one for which there is no evidence of risk in humans; either animal findings show risk, but human findings do not; or, if no adequate human studies have been done, animal findings are negative (Odalovic 2012).

2. Aspirin may increase bleeding probability in a pregnant woman and in the neonate (Askie 2007).

3. Steroids are recommended for only short-term administration due to potential side effects (Saeki 2009). These include diabetes, hypertension, gastric ulcers, osteoporosis, skin atrophy, Cushing's syndrome, glaucoma, and growth retardation (Simon 2014).

4. Opioid antagonists: the limited data on buprenorphine exposure during pregnancy show no increased risk of teratogenic effects, whereas naloxone is not expected to be involved in an increased risk of adverse pregnancy outcomes (Poon 2014).

5. Antidepressants: evidence of congenital heart defects (CHD) related to selective serotonin reuptake inhibitors (SSRI) in early pregnancy exposure have led to recommendations to

weigh benefits and risks carefully (Wemakor 2015). Paroxetine, a serotonin reuptake inhibitor, starts with small doses, such as 5 mg to 10 mg nightly, which will cause fewer side effects than higher doses. Effects can be observed within 24 to 48 hours (Seccareccia 2011). The revision of the pharmacovigilance studies indicate that most of the SSRIs have a teratogenic risk the same as unexposed controls. For other antidepressants (tricyclics, mirtazapine, venlafaxine, escitalopram, duloxetine) the evidences on the level of risk are still numerically inconstant and need to be clarified by further research (Goracci 2015).

How the intervention might work

Pharmacological interventions

Topical drugs

1. Cooling agents (e.g. phenol, menthol, and camphor) evoke nerve fibres which transmit a cold sensation, which substitutes the itch sensation. Cooling the skin provides remarkable itching relief. Calamine, comprising phenol 0.5%, is a pink-coloured lotion that is cosmetically unacceptable to most people. Menthol 1%, an alcohol derived from mint oils, is a safe therapy that has been used for centuries (Lynde 2008). Camphor 0.1% to 3% is a ketone acquired from the camphor tree (Hercogova 2005).

2. Topical anaesthetics agents (e.g. benzocaine, lidocaine, pramoxine, and EMLA) have been shown to have antipruritic properties (Yosipovitch 1997).

3. Topical steroids reduce itching by reducing local inflammation. Thus it has no benefit in non-inflammatory itch (Elmariah 2011).

4. Capsaicin has an inhibitory effect in histamine-induced itching (Weisshaar 1998) resulting from desensitisation of the neurons in the skin by activating the release of substance P, a mediator in the transmission of itching (Tarnig 1996). Furthermore, it is an effective topical treatment for haemodialysis-induced itching in patients with end-stage renal disease (Makhlough 2010), skin disorder (Yosipovitch 2003), and pruritus ani (Lysy 2003). In contrast to these assertions, however, a systematic review of the use of topical capsaicin in itching concluded that there is no convincing evidence for the use of capsaicin to treat itching in any medical condition (Gooding 2010).

Systemic drugs

1. Antihistamines: H1-receptor antagonists have a limited effect in the management of itching, because histamine does not have a major role in itching other than in urticaria (Yosipovitch 2013). The American College of Obstetricians and

Gynecologists and The American College of Allergy, Asthma and Immunology have recommended chlorpheniramine and tripeleminamine as the antihistamines of choice in pregnancy. Moreover, pregnant women who cannot tolerate or do not respond to maximal doses of these drugs may use cetirizine and loratadine instead (Kar 2012). Other studies suggest that there is insufficient evidence to support the first-line use of cetirizine and loratadine during pregnancy and recommend first considering chlorpheniramine, tripeleminamine, or hydroxyzine if an antihistamine is needed during pregnancy (Gilbert 2005).

2. Aspirin (acetylsalicylic acid) with serotonin antagonists reduces itching (or pruritus) in patients with polycythaemia vera (Krajnik 2001). The FDA recommended that pregnant women do not use aspirin during the 1st trimester and last three months of pregnancy (Bloor 2013).

3. Steroids bind to regulatory elements of genes of many mediators, i.e. cytokines, chemokines, and adhesion units by inflammatory cells and resident cells resulting in resolution of inflammation (Simon 2014).

4. Opioid antagonists reduce itching by activation of spinal cord opioid receptors on the pain-transmitting neurons, which induce analgesia as well as itching (Xander 2013).

5. Antidepressants affect the cerebral cortex reducing the perception of pruritus (Parel 2010). Selective serotonin reuptake inhibitors (SSRIs) inhibit serotonin reuptake into the presynaptic cell and increasing the level of serotonin in the synaptic cleft (Xander 2013). Serotonin might have a role in pruritus secondary to malignant disease, cholestasis, uremia, and opioids (Seccareccia 2011).

Why it is important to do this review

Generalised itching is common in the later months of pregnancy, with associated impairment to quality of life, poor sleep, and can be very frustrating for pregnant women. Many drugs used in pregnancy carry a risk for teratogenicity, thus careful risk and benefit assessment is vital for the clinical management of these women. There is a need for a systematic review to evaluate the effectiveness and safety of interventions for treating itching (or pruritus) in pregnancy.

This review plans to update and expands the scope of an earlier Cochrane review on 'Antihistamines versus aspirin for itching in late pregnancy' (Young 2010).

OBJECTIVES

To assess the effectiveness and safety of pharmacological interventions for treating generalised itching (not caused by systemic disease or skin lesions) in pregnancy.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include all published, unpublished and ongoing randomised controlled trials (RCTs) evaluating interventions for itching in pregnancy.

Quasi-RCTs, cluster-RCTs, RCTs using a cross-over design, and studies reported in abstract form (without full text) were not eligible for inclusion. It is unlikely that cross-over designs will be a valid study design for Pregnancy and Childbirth reviews, and so will be excluded if they are identified in future updates of this review.

Types of participants

Pregnant women with normal liver function complaining of itching (defined as an unpleasant sensation which provokes a desire to scratch).

This review covers generalised itching in pregnant women who do not have systemic disease or skin lesions (including atopic rashes). We planned to exclude studies of pregnant women with intra-hepatic cholestasis (as this is covered by another Cochrane review (Gurung 2013)), pregnancy-related dermatoses and generalised itching with systemic disease.

Types of interventions

All pharmacological interventions for treating itching in pregnancy, not only one intervention versus another intervention for treating itching but also intervention versus placebo/no intervention or combined interventions.

Types of outcome measures

Primary outcomes

1. Relief of itching (as determined by the study authors)

Secondary outcomes

1. Women's satisfaction (as determined by the study authors)
2. Sleep disturbance (as determined by the study authors)
3. Adverse effects (maternal and fetal)

Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (28 January 2016).

The Register is a database containing over 20,000 reports of controlled trials in the field of pregnancy and childbirth. For full search methods used to populate the Pregnancy and Childbirth Group's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL, the list of hand-searched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about the [Cochrane Pregnancy and Childbirth Group](#) in *The Cochrane Library* and select the '*Specialized Register*' section from the options on the left side of the screen.

Briefly, the Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth Group review topic (or topics), and is then added to the Register. The Trials Search Co-ordinator searches the Register for each review using this topic number rather than keywords. This results in a more specific search set which has been fully accounted for in the relevant review sections (Included, Excluded, Awaiting Classification or Ongoing).

Searching other resources

We searched the reference lists of retrieved studies. We did not apply any language or date restrictions.

Data collection and analysis

The methods section of this review was based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Selection of studies

Two review authors, Phassawan Rungsiprakarn (PR) and Pisake Lumbiganon (PL) independently assessed for inclusion the one potential study identified as a result of the search strategy. The study was excluded.

Full methods of data collection and analysis to be used in future updates of this review are provided in [Appendix 1](#).

RESULTS

Description of studies

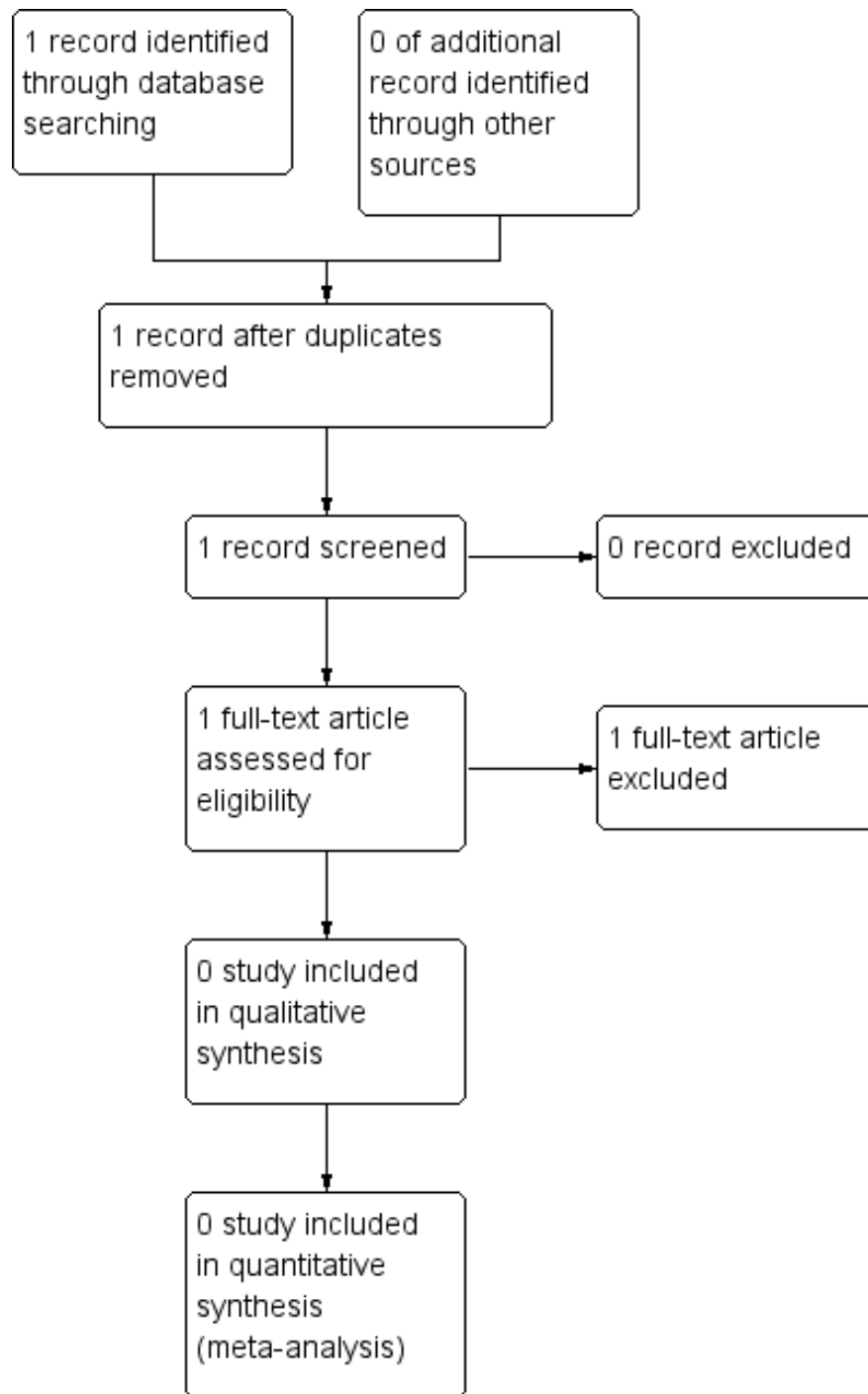
See: [Characteristics of excluded studies](#).

No studies were included.

Results of the search

See: [Figure 1](#).

Figure 1. Study flow diagram.



The search of the Cochrane Pregnancy and Childbirth Group's Trials Register identified only one report (Read 1977), which we excluded.

Included studies

There are no included studies.

Excluded studies

One trial was excluded (Read 1977) - this trial compared a histamine with aspirin but used a cross-over design (and this study design is not eligible for inclusion in this review).

Risk of bias in included studies

There are no included studies.

Effects of interventions

There are no included studies.

DISCUSSION

Generalised itching is distressing, causes constant discomfort, sleep disturbance and therefore can have a very negative effect on pregnant women's general well being, with a prevalence of around 17% to 18% (Kroumpouzos 2002; Schroeder 2000; Weisshaar 2009). Despite this, there were no randomised controlled trials that evaluated the effectiveness of pharmacological interventions to relieve the condition that could be included in this systematic review. The search strategy identified one trial report (Read 1977) which we excluded.

Potential biases in the review process

We attempted to minimise bias in the review process wherever possible and followed Cochrane methodology. We carried out an extensive search for studies (without any restrictions on language or date), two review authors independently assessed the one identified trial for inclusion/exclusion.

Agreements and disagreements with other studies or reviews

There are no other systematic reviews assessing the effectiveness and adverse effects of pharmacological interventions for generalised itching (not caused by systemic disease or skin lesions) during pregnancy. However there is a Cochrane review by Gurung 2013 which evaluates pharmacological interventions for treating pregnant women with cholestasis (a condition which is excluded from our review). Gurung 2013 indicated that ursodeoxycholic acid (UDCA) significantly improves pruritus but had insufficient evidence about the effectiveness of S-adenosylmethionine (SAME), guar gum, activated charcoal, dexamethasone, cholestyramine, Salvia, Yinchenghao decoction (YCHD), Danxioling and Yiganling, or Yiganling alone or in combination in treating itching in women with obstetric cholestasis.

AUTHORS' CONCLUSIONS

Implications for practice

There are no included studies in this review. There is no evidence from randomised controlled trials to guide practice in terms of the effectiveness and safety of pharmacological interventions for generalised itching (not caused by systemic disease or skin lesions) in pregnancy.

Implications for research

Generalised itching (not caused by systemic disease or skin lesions) is quite a common symptom in pregnancy. Well-designed randomised controlled trials are needed in order to evaluate the effectiveness of topical and systemic pharmacological interventions as well as any adverse effects of the interventions. Such studies should consider important outcomes such as relief of itching, women's satisfaction, sleep disturbance, adverse effects.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Read 1977	This study was a cross-over trial that compared a histamine with aspirin but the study design is not eligible for inclusion in this review

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix I. Methods of data collection and analysis to be used in future updates of this review

Data collection and analysis

Selection of studies

Two review authors, Phassawan Rungsiprakarn (PR) and Pisake Lumbiganon (PL) will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult a third review author, Malinee Laopaiboon (ML). We will create a study flow diagram to map out the number of records identified, included and excluded.

Data extraction and management

We will design a form to extract data. For eligible studies, PR, Ussanee S Sangkomkamhang (US) and ML will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult PL. We will enter data into Review Manager software ([RevMan 2014](#)) and check for accuracy. When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors, PR and ML, will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We will resolve any disagreement by discussion or by consulting PL.

(1) Random sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We will assess the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We will assess the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.

We will assess methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We will assess the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We will describe for each included study any important concerns we have about other possible sources of bias.

We will assess whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and

direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - *see Sensitivity analysis*.

Assessing the quality of the body of evidence using the GRADE approach

The quality of the evidence will be assessed using the GRADE approach as outlined in the [GRADE handbook](#) in order to assess the quality of the body of evidence relating to the following outcomes. We have selected the following outcomes for the main comparisons.

1. Relief of itching (as determined by the study authors)
2. Women's satisfaction (as determined by the study authors)
3. Sleep disturbance (as determined by the study authors)
4. Adverse effects (maternal and fetal)

We will use the [GRADEpro](#) Guideline Development Tool to import data from Review Manager 5.3 ([RevMan 2014](#)) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes will be produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

For dichotomous data we will present results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods

Unit of analysis issues

Cluster-randomised trials

We will not include cluster-randomised trials in this review.

Cross-over trials

We will not include cross-over trials in this review.

Multi-armed trials

We will include multi-armed trials in the analyses along with individually-randomised trials. We will include the relevant intervention groups in a pair-wise comparison of intervention groups that meet the criteria for including studies in the review. We will combine groups to create a single pair-wise comparison using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the T^2 , I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if an I^2 is greater than 30% and either a T^2 is greater than zero, or there is a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We will carry out statistical analysis using the Review Manager software ([RevMan 2014](#)). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average of the range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

If we use random-effects analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of T^2 and I^2 .

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

We plan to carry out the following subgroup analyses:

1. short-term use versus prolonged use;
2. different routes of interventions such as oral route versus topical route;
3. trimester of pregnancy; first versus second trimester, first versus third trimester, and second versus third trimester.

Planned sensitivity analysis will be restricted to the review's primary outcomes.

We will assess subgroup differences by interaction tests available within RevMan ([RevMan 2014](#)). We will report the results of subgroup analyses quoting the χ^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We will carry out sensitivity analyses for only primary outcomes to explore the effect of trial quality based on concealment of allocation. We will exclude trials rated as 'high risk of bias' or 'unclear risk of bias' for allocation concealment in order to assess for any substantive difference to the overall result.

CONTRIBUTIONS OF AUTHORS

Phassawan Rungsiprakarn (PR) developed the protocol. Malinee Laopaiboon (ML), Pisake Lumbiganon (PL) and Ussanee Sangkomkamhang (US) edited and commented on the protocol.

For the review, PR and PL independently screened the one article identified. ML summarised the results. PR drafted the review. All review authors commented and finalised the review. For the updated review, PR and US will independently extract new data and update the review. ML will add a GRADE summary. All review authors will comment and finalise the updated review.

DECLARATIONS OF INTEREST

Phassawan Rungsiprakarn: none known.

Malinee Laopaiboon: none known.

Ussanee S Sangkomkamhang: none known.

Pisake Lumbiganon: none known.

SOURCES OF SUPPORT

Internal sources

- Faculty of Medicine, Khon Kaen University, Thailand.
- Faculty of Public Health, Khon Kaen University, Thailand.
- Cochrane Thailand, Thailand.
- Khon Kaen Hospital, Khon Kaen, Ministry of Public Health, Thailand.

External sources

- Thailand Research Fund/Distinguished Professor Award, Thailand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In our published protocol ([Rungsiprakarn 2014](#)), the methods section ('types of studies' and 'types of interventions') stated that we would evaluate interventions during 'late' pregnancy; we have now deleted the word 'late' to include the entire pregnancy period. We have also added text to 'types of participants' to clarify conditions that are not covered in this review (this information was included in our published protocol (under background/description of the condition), but not within the methods section).

The contact person for the review has changed from Phassawan Rungsiprakarn to Malinee Laopaiboon.

We have added methods for the use of the GRADE approach to examine the quality of the body of evidence and the inclusion of a 'Summary of findings' table (see [Appendix 1](#)).

In our methods/types of participants we have clarified that this review will include generalised itching in pregnant women who do not have systemic disease or skin lesions (including atopic rashes). This review will not include studies involving pregnant women with intrahepatic cholestasis (covered by another Cochrane review ([Gurung 2013](#))), or pregnancy-related dermatoses and generalised itching with systemic disease.

In our methods/types of interventions we have clarified that the intervention is for treating itching in pregnancy (not just late pregnancy) as listed in our published protocol.

In our methods for subgroup analysis and investigation of heterogeneity (see [Appendix 1](#)), we have clarified that planned subgroup analyses will be restricted to the review's primary outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

Pregnancy Complications [*drug therapy; etiology]; Pruritus [*drug therapy; etiology]

MeSH check words

Adult; Female; Humans; Pregnancy



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Effectiveness of tranexamic acid in reducing blood loss during cytoreductive surgery for advanced ovarian cancer (Review)

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	3
BACKGROUND	6
OBJECTIVES	7
METHODS	7
RESULTS	9
Figure 1.	10
Figure 2.	12
DISCUSSION	14
AUTHORS' CONCLUSIONS	15
ACKNOWLEDGEMENTS	15
REFERENCES	16
CHARACTERISTICS OF STUDIES	17
DATA AND ANALYSES	21
Analysis 1.1. Comparison 1 Estimated total blood loss (mL), Outcome 1 Estimated total blood loss (mL).	22
Analysis 2.1. Comparison 2 Number of transfused units of blood components, Outcome 1 Number of transfused units of RBC.	23
Analysis 2.2. Comparison 2 Number of transfused units of blood components, Outcome 2 Number of transfused units of plasma.	23
Analysis 3.1. Comparison 3 Rate of blood component transfusion, Outcome 1 Red blood cell transfused women.	24
Analysis 3.2. Comparison 3 Rate of blood component transfusion, Outcome 2 Plasma transfused women.	24
Analysis 4.1. Comparison 4 Incidence of reoperation, Outcome 1 Reoperation.	25
Analysis 5.1. Comparison 5 Incidence of readmission, Outcome 1 Readmission.	25
Analysis 6.1. Comparison 6 Incidence of thromboembolic events, Outcome 1 Venous thromboembolic events.	26
Analysis 6.2. Comparison 6 Incidence of thromboembolic events, Outcome 2 Arterial thromboembolic events.	26
ADDITIONAL TABLES	26
APPENDICES	27
WHAT'S NEW	30
CONTRIBUTIONS OF AUTHORS	30
DECLARATIONS OF INTEREST	31
SOURCES OF SUPPORT	31
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	31
NOTES	33
INDEX TERMS	33

Effectiveness of tranexamic acid in reducing blood loss during cytoreductive surgery for advanced ovarian cancer

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ABSTRACT

Background

Ovarian cancer is the third most common gynaecological cancer worldwide, with an age-standardised incidence rate of 6.1 per 10,000 women. Standard therapy for advanced epithelial ovarian cancer (EOC) includes a combination of cytoreductive surgery and platinum-based chemotherapy. Cytoreductive surgery aims to remove as much of the visible tumour as possible. As extensive intraperitoneal metastases are typical of advanced EOC, cytoreductive surgery is usually an extensive procedure with the risk of excessive bleeding. Tranexamic acid given perioperatively is effective in reducing blood loss and allogeneic blood transfusion requirements in a variety of surgical settings. Therefore, tranexamic acid seems to be a promising agent for minimising blood loss and the need for blood transfusion among women with advanced EOC undergoing cytoreductive surgery.

Objectives

To assess the effects of tranexamic acid for reducing blood loss associated with cytoreductive surgery in women with advanced EOC (stage III to IV).

Search methods

We searched the Cochrane Gynaecological, Neuro-oncology and Orphan Cancers Trial Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 5, 2015), MEDLINE, EMBASE and conference proceedings to May 2015. We also checked registers of clinical trials, citation lists of included studies, key textbooks and previous systematic reviews for potentially relevant studies.

Selection criteria

We included randomised controlled trials (RCTs) comparing tranexamic acid given during surgery versus placebo or no treatment, in adult women diagnosed with advanced EOC.

Data collection and analysis

Two review authors (CK, AS) independently selected potentially relevant trials, extracted data, assessed risk of bias, compared results and resolved disagreements by discussion.

Main results

We found only one study that met our inclusion criteria. This was a randomised double blind, placebo-controlled multicentre study conducted to evaluate the effectiveness of a single dose of intravenous tranexamic acid (15 mg/kg body weight) versus placebo, given immediately before surgery for reducing blood loss and the need for red blood cell transfusion. The mean total estimated blood loss was 668.34 mL and 916.93 mL for participants assigned to tranexamic acid and placebo groups, respectively. The mean difference (MD) of total estimated blood loss between the groups did not show a clinically important effect (MD = 248.59 mL; 95% confidence interval (CI) = -550.9 to 53.79; one study, 100 participants; moderate quality evidence). The mean number of transfused units of blood components was not different between the two groups (low quality evidence). There were no noted differences in the incidence of reoperation, readmission or thromboembolic events (very low quality evidence). We considered the methodology of the included study to be at low risk of selection, detection, and reporting biases. However, we were concerned about an imbalance of some baseline characteristics between the groups, and as there was no protocol for blood transfusion, the rate of blood transfusion may vary depending on the practice of each participating hospital.

Authors' conclusions

Currently, there is insufficient evidence to recommend the routine use of tranexamic acid for reducing blood loss in women undergoing cytoreductive surgery for advanced EOC, as only limited data are available from a single, low quality RCT at low overall risk of bias.

PLAIN LANGUAGE SUMMARY

Does tranexamic acid given before an operation reduce blood loss for women with advanced ovarian cancer?

The issue:

Cytoreductive surgery (also called debulking) is a standard surgical procedure for advanced epithelial ovarian cancer. During surgery, the aim is to remove not only the ovaries, but also the uterus, fallopian tubes, and as much of the visible tumour as possible. Blood loss during cytoreductive surgery has long been recognised as a contributor to prolonged recovery time.

The aim of the review:

We evaluated the effectiveness and safety of tranexamic acid for reducing blood loss during cytoreductive surgery in women with advanced epithelial ovarian cancer. We searched for scientific research studies up to May 2015 and found only one randomised controlled trial – considered the gold standard for study design – that assessed a single dose of tranexamic acid given intravenously before the start of surgery versus a placebo in women undergoing cytoreductive surgery for clinically suspected advanced advanced epithelial ovarian cancer.

What are the main findings and conclusion?

Although tranexamic acid did numerically reduce blood loss, there was no clinical benefit, as the difference in blood loss was minimal, and there was no difference in need for blood transfusion, suggesting that this level of blood loss did not make a difference to the patient's well-being. Additionally, there was incomplete and limited evidence regarding tranexamic acid-related adverse events, so we can say little about whether tranexamic acid is safe for women with advanced ovarian cancer. The evidence we found from a single study was therefore insufficient to support routinely giving prophylactic tranexamic acid for cytoreductive surgery. This review indicates the need for future good quality, well-designed randomised controlled trials to provide more evidence on the effectiveness, safety and appropriate administration of tranexamic acid.

Quality of evidence:

The quality of the evidence was variable; therefore the overall the strength of the evidence reported in this review is low, as it is based on only one small randomised controlled study.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Effectiveness of tranexamic acid in reducing blood loss during cytoreductive surgery for advanced ovarian cancer						
Patient or population: adult women with advanced EOC undergoing cytoreductive surgery (one randomised trial available) Settings: 2 university hospitals and 2 central hospitals in the southeast health region of Sweden Intervention: a single dose of tranexamic acid (15 mg/kg body weight, 100 mg/mL tranexamic acid) immediately before the start of surgery Comparison: placebo prepared in the identical package Note: The trial protocol allowed the use of supplemental tranexamic acid (20% of participants of each group received supplemental tranexamic acid during surgery)						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Tranexamic acid				
Estimated total blood loss (mL)	Mean 916.93	Mean 248.59 lower (95% CI, 550.9 lower to 53.8 higher)	MD -248.59 (– 550.97 to 53.79)	100 (1 study)	⊕⊕○○ low ^{1,2}	Trial authors provided additional data. See Table 1 .
Number of transfused units of red blood cell (RBC)	Mean 0.76	Mean 0.30 lower (95% CI, 0.88 lower to 0.28 higher)	MD – 0.30 (–0.88 to 0.28)	100 (1 study)	⊕⊕○○ low ^{1,3}	38 units and 53 units of RBC were transfused to women in the tranexamic acid and placebo groups, respectively. Trial authors provided additional data regarding to mean number of transfused units . See Table 1
Number of transfused units of plasma	Mean 0.28	Mean 0.12 lower (95% CI, 0.41 lower to 0.17 higher)	MD – 0.12 (– 0.41 to 0.17)	100 (1 study)	⊕⊕○○ low ^{1,3}	Trial authors provided additional data. See Table 1 .

Rate of RBC transfusion (total number of participants who required at least one unit of red blood cell transfusion) Time: perioperative and postoperative periods	44 per 100	30 per 100 (18 to 51)	RR 0.68 (0.40 to 1.15)	100 (1 study)	⊕⊕○○ low ^{1,3}	
Rate of plasma transfusion (total number of participants who required at least one unit of plasma transfusion) Time: perioperative and postoperative periods	18 per 100	8 per 100 (3 to 24)	RR 0.44 (0.15 to 1.35)	100 (1 study)	⊕⊕○○ low ^{1,3}	-
Reoperation (Number of participants with at least one reoperation) Time: perioperative periods	12 per 100	10 per 100 (3 to 31)	RR 0.83 (0.27 to 2.55)	100 (1 study)	⊕○○○ very low ^{1,2,4}	-
Readmission (Number of participants with at least one readmission) Time: perioperative periods	8 per 100	22 per 100 (7 to 64)	RR 2.75 (0.94 to 8.06)	100 (1 study)	⊕○○○ very low ^{1,2,4}	-
Venous thromboembolic events (number of participants with at least one venous thromboembolic	8 per 100	4 per 100 (1 to 21)	RR 0.50 (0.10 to 2.61)	100 (1 study)	⊕○○○ very low ^{1,2,4,5}	-

events) Time: 5-week follow-up visit						
Arterial thromboembolic events (number of participants with at least one venous thromboembolic events) Time: 5-week follow-up visit)	2 per 100	1 per 100 (0 to 16)	RR 0.33 (0.01 to 7.99)	100 (1 study)	⊕○○○ very low ^{1,2,4,5}	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD**: mean difference; **RR**: risk ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹Based on the high risk of attrition bias and baseline imbalance in allocation.

²Wide confidence interval.

³The included study had no well-defined criteria or protocol for blood transfusion.

⁴Small number of events in the analysis.

⁵Only about 60% of participants in both arms underwent duplex ultrasound examination to evaluate lower extremity venous thrombosis.

BACKGROUND

Description of the condition

Ovarian cancer is the third most common gynaecological cancer worldwide, with an age-standardised incidence rate of 6.1 per 10,000 women (GLOBOCAN 2012). Epithelial ovarian cancer (EOC), arising from the surface layer of the ovary, accounts for more than 90% of all ovarian cancer and is, in the developed world, the leading cause of death among women with gynaecological cancer, with a mortality rate of more than 60%. This is largely because most women with EOC are diagnosed when the cancer is already at an advanced stage (Jemal 2008). Extensive intraperitoneal metastases are typical of advanced EOC.

Standard therapy for advanced EOC consists of cytoreductive surgery and platinum-based chemotherapy. During cytoreductive surgery (also called debulking), the aim is to remove not only the ovaries but also the uterus, fallopian tubes, and as much of the visible tumour as possible. Studies have noted that the volume of residual disease after cytoreductive surgery is an important independent prognostic factor for survival in women with EOC (Chi 2012; Vergote 2010). The median overall survival of women with advanced EOC, stratified by volume of residual disease following surgery, is 78 months for women with no macroscopic disease, 50 months when the residual disease is less than 1 cm, and 36 months when the residual disease is more than 1 cm (Chi 2012). Therefore, cytoreductive surgery, with the aim of complete resection of all visible tumour, is central to the treatment of EOC. Cytoreductive surgery can be an extensive procedure, and approximately 4.1% to 7.4% of women with advanced EOC experience excessive bleeding during the intervention, with a red blood cell transfusion rate of 30% to 40% (Lundin 2014; Vergote 2010).

Description of the intervention

Tranexamic acid, a 4-aminomethyl cyclohexane-carboxylic acid, is a synthetic lysine amino acid derivative that exerts an antifibrinolytic effect through the reversible blockade of the lysine-binding sites on the plasminogen molecule to fibrin, thereby inhibiting clot degradation. Compared to other synthetic lysine analogues, tranexamic acid has a higher antifibrinolytic efficacy in peripheral tissue and a longer half-life at 3.1 hours (McCormack 2012). Tranexamic acid can be administered orally, intravenously and topically. Its role for preventing and treating excessive blood loss continues to receive attention in various surgical and trauma settings (Ker 2013; Kongnyuy 2014; Novikova 2015; Perel 2013; Roberts 2015).

How the intervention might work

Tissue injury triggers the activation of the blood clotting (haemostatic) system. Initially, the formation of thrombin stimulates the

conversion of fibrinogen into fibrin. The fibrinolytic processes are subsequently activated to degrade (break down) the fibrin clot in order to maintain vascular patency (when blood vessels are unblocked or unobstructed). Fibrinolysis begins after the conversion of plasminogen into plasmin, an enzyme necessary in the breakdown of fibrin. It is stimulated by tissue plasminogen activator (t-PA) and urokinase plasminogen activator, endogenous activators of plasminogen. Plasmin activity is also modulated by various naturally occurring plasminogen activator inhibitors to achieve equilibrium between clot formation and breakdown (McCormack 2012).

Although fibrinolysis is a part of a normal physiological response to tissue damage, any disturbance in the balance between activators and inhibitors of the fibrinolytic system may result in excessive bleeding. During surgical procedures, increased activity of plasminogen activators also increases the consumption of the plasminogen activator inhibitor and in turn the premature breakdown of fibrin. In procedures that result in extensive tissue damage, this process may be excessive and result in hyperfibrinolysis. Tranexamic acid works by preventing the breakdown of blood clots and so reduces bleeding. As a result of inhibiting fibrinolysis, there is a theoretical possibility of an increased risk of thromboembolic events (blood clots that block vessels (thrombus) can break loose and be carried by the blood stream to other organs (embolism)). However, these adverse events are relatively rare. More common adverse events of tranexamic acid include nausea, vomiting, diarrhoea, dyspepsia and headache (McCormack 2012).

A number of Cochrane systematic reviews in a variety of surgical settings have reported on the perioperative administration of tranexamic acid with the aim of reducing blood loss and the need for blood transfusion (Kongnyuy 2014; Novikova 2015; Perel 2013; Roberts 2015).

In trauma patients, tranexamic acid reduced the risk of death due to bleeding by 15% (risk ratio (RR) 0.85, 95% confidence interval (CI) 0.76 to 0.96; Roberts 2015). In the emergency and urgent surgery setting, tranexamic acid reduced the probability of receiving a blood transfusion by 30% (RR 0.70, 95% CI 0.52 to 0.94; Perel 2013). The amount of postpartum blood loss also decreased in women receiving tranexamic acid compared to women receiving placebo (mean difference 75.17 mL; 95% CI 108.23 to 42.12 mL), regardless of route of delivery (Novikova 2015). Additionally, compared with placebo, tranexamic acid is an effective intervention to reduce blood loss during myomectomy for fibroids (mean difference (MD) 243 mL 95% CI 460.02 to 25.98 mL; Kongnyuy 2014). As a topical application, tranexamic acid reduces blood transfusion rates in surgical patients by 45% (RR 0.55, 95% CI 0.55 to 0.46; Ker 2013).

Why it is important to do this review

Excessive blood loss during extensive surgery puts women at risk of death and increases recovery times. Blood products are a scarce

resource and are not without risks. Some previous studies have reported an independent association between receiving a perioperative blood transfusion and a higher risk of cancer recurrence (De Oliveira 2012; Schiergens 2015). As blood loss during cytoreductive surgery for ovarian cancer can be high, tranexamic acid seems to be a promising agent to reduce both it and the need for transfusion.

We hypothesise that tranexamic acid effectively reduces blood loss and blood transfusion requirements in women undergoing cytoreductive surgery for advanced EOC. However, to date there has been no systematic review evaluating the effectiveness of tranexamic acid to reduce blood loss and allogeneic blood transfusion requirements in cytoreductive surgery for advanced EOC.

OBJECTIVES

To assess the effects of tranexamic acid for reducing blood loss associated with cytoreductive surgery in women with advanced EOC (stage III to IV).

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs).

Types of participants

Women aged 18 years or older undergoing cytoreductive surgery for advanced ovarian cancer. We present details of the staging classification of ovarian cancer in [Appendix 1 \(Prat 2015\)](#).

Types of interventions

We planned to include studies comparing tranexamic acid given during surgery versus placebo or no treatment.

Types of outcome measures

Primary outcomes

- Estimated blood loss (mL)

Secondary outcomes

- Units of blood components transfused (e.g. red blood cell and plasma)
- Length of surgery (min)
- Postoperative haemoglobin (g/L)
- Incidence of reoperation
- Incidence of readmission
- Length of hospital stay (days)
- Incidence of venous thromboembolic events (e.g. venous thrombosis, pulmonary embolism)
- Incidence of arterial thromboembolic events (e.g. arterial thrombosis, myocardial infarction, stroke)
- Incidence of nausea/vomiting/diarrhoea
- Incidence of neurological events (e.g. headache, seizure, eye or eyesight problems)
- The severity of tranexamic acid-related adverse events, as categorised according to Common Terminology Criteria for Adverse Events (CTCAE 2010)

Search methods for identification of studies

Electronic searches

We searched the following electronic databases:

- Cochrane Central Register of Controlled Trial (CENTRAL) (2015, Issue 5)
- MEDLINE (1946 to May week 5, 2015)
- EMBASE (1980 to 2015 week 23)

We present the CENTRAL, MEDLINE and EMBASE search strategies in [Appendix 2](#), [Appendix 3](#) and [Appendix 4](#), respectively.

Searching other resources

Unpublished and grey literature

We searched the following for ongoing trials.

- Metaregister (<http://www.controlled-trials.com/rct>).
- Physicians Data Query (<http://www.nci.nih.gov>).
- <http://www.clinicaltrials.gov>.
- <http://www.cancer.gov/clinicaltrials>.
- World Health Organization (WHO) International Clinical Trial Registry (<http://apps.who.int/trialsearch/Default.aspx>).

We searched electronic databases including Greynet.org (<http://www.greynet.org>) and the Ohio College Library Center (OCLC) WorldCat Dissertations and Theses (WorldCatDissertations) (<https://www.oclc.org/support/services/firstsearch/documentation/dbdetails/details/WorldCatDissertations.en.html>) to identify the possible relevant conference abstracts and proceedings.

Handsearching

We handsearched reports of conferences from the following sources.

- *Gynecologic Oncology* (Annual Meeting of the Society of Gynecologic Oncology).
- *International Journal of Gynecological Cancer* (Annual Meeting of the International Gynecological Cancer Society).
- British Cancer Research Meeting.
- American Association for Clinical Research (AACR) Meeting.
- Annual Meeting of the European Society of Medical Oncology (ESMO).
- Annual Meeting of the American Society of Clinical Oncology (ASCO).
- Annual Meeting of the British Gynaecological Cancer Society (BGCS).
- Biennial Meeting of the Asian Society of Gynecologic Oncology (ASGO).
- Biennial Meeting of Asia and Oceania Federation of Obstetrics and Gynaecology (AOFOG).
- Biennial Meeting of the European Society of Gynaecologic Oncology (ESGO).

We also checked the citation lists of the included study and key textbooks for potentially relevant references.

We searched for papers in all languages and would have had them translated, if necessary.

Data collection and analysis

Selection of studies

Before examining the identified trials for possible inclusion, we developed and piloted a data collection form. We downloaded all titles and abstracts retrieved by electronic searching to a reference management database ([EndNote](#)) and removed duplicates. Two review authors (CK and AS) examined the remaining references independently. We excluded studies that clearly did not meet the inclusion criteria. We obtained full-text copies of potentially relevant references. Two review authors (CK and AS) independently assessed the eligibility of the retrieved reports/publications. We resolved any disagreement through discussion or, if required, we consulted a third person (PL). We identified and excluded duplicates and collated multiple reports of the same study so that each study rather than each report was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table ([Liberati 2009](#)).

Data extraction and management

Two review authors (CK and AS) independently extracted study characteristics and outcome data from included studies onto a pre-piloted data collection form. We noted in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We also noted the details of trial method, participant characteristics, intervention, and outcomes in the [Characteristics of included studies](#) table. We resolved disagreements by consensus or by involving a third person (PL). One review author (ML) transferred data into the Review Manager (RevMan) file ([RevMan 2014](#)). We double checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (PL) spot checked study characteristics for accuracy against the trial report.

For included studies, we extracted the following data.

- Author, year of publication and journal citation (including language).
- Country.
- Setting.
- Inclusion and exclusion criteria.
- Study design, methodology.
- Study population.
 - Total number enrolled.
 - Patient characteristics.
 - Age.
 - Comorbidities.
 - Other baseline characteristics.
 - Histopathological type of ovarian cancer (according to World Health Organization classification system; [Kaku 2003](#)).
 - Stage of ovarian cancer.
 - Completeness of debulking and diameter of residual tumour deposits, if present (cm).
- Intervention details: tranexamic acid.
 - Dose of tranexamic acid.
 - Administration route and frequency, i.e. intravenous (single dose, multiple dose), oral or topical administration.
 - Timing of administration in relation to the start of the operation (knife-to-skin).
- Comparison: usual care or placebo.
 - Definition/details.
 - Additional information if appropriate.
- Outcomes: For each outcome, we extracted the outcome definition and unit of measurement (if relevant).
- Results: We extracted the number of participants allocated to each intervention group, the total number analysed for each outcome, and the missing participants. For adjusted estimates, we recorded adjusted results in analyses.
- Notes: funding of the trial, and notable conflicts of interest of the trial authors.

Results were extracted as follows.

- For dichotomous outcomes (e.g. readmission, reoperation and adverse events): We extracted the number of participants in

each treatment arm who experienced the outcome of interest and the number of participants assessed at the endpoint in order to estimate a risk ratio.

- For continuous outcomes (e.g. amount of blood loss and unit(s) of blood component transfused): We extracted the mean and standard deviation (SD) of the outcome of interest and the number of participants assessed in order to estimate the mean difference (MD) between treatment arms.

Where possible, all data extracted were those relevant to an intention-to-treat analysis, in which participants were analysed in the groups to which they were assigned.

Assessment of risk of bias in included studies

We assessed and reported on the methodological risk of bias of the included studies according to Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), which recommends the explicit reporting of the following individual elements for RCTs.

1. Selection bias: random sequence generation and allocation concealment.
2. Performance bias: blinding of participants and personnel (participants and treatment providers).
3. Detection bias: blinding of outcome assessment.
4. Attrition bias: incomplete outcome data.
5. Reporting bias: selective reporting of outcomes.
6. Other bias.

Two review authors (CK, AS) applied the 'Risk of bias' tool independently, and we resolved differences by discussion or by appeal to a third review author (PL or ML). We judged each item as being at high, low or unclear risk of bias as set out in the criteria shown in [Appendix 5](#) (Higgins 2011). We provided a quote from the study report or a statement as justification for our judgement. We summarised results in a 'Risk of bias' summary figure.

Measures of treatment effect

We used the following measures of the effect of treatment:

- For dichotomous outcomes, such as incidence of re-admission, we used number of events and number of participants assessed in both the intervention and comparison groups to calculate the risk ratio (RR) and 95% confidence interval (CI).

- For continuous outcomes, such as estimated blood loss, we used the mean, standard deviation (SD), and number of participants assessed in both the intervention and comparison groups to calculate the mean difference (MD) with a 95% CI.

Dealing with missing data

We did not impute missing outcome data and attempted to contact trial authors to obtain missing data if necessary.

Data synthesis

We identified only one included trial, so it was not possible to perform meta-analyses. Therefore it was not relevant to carry out the following procedures: assessing heterogeneity between the results of trials, assessing reporting biases using funnel plots, or conducting any subgroup analyses or sensitivity analyses. In future updates of the review, we will employ the methods stated in the [Differences between protocol and review](#) if we identify additional studies.

RESULTS

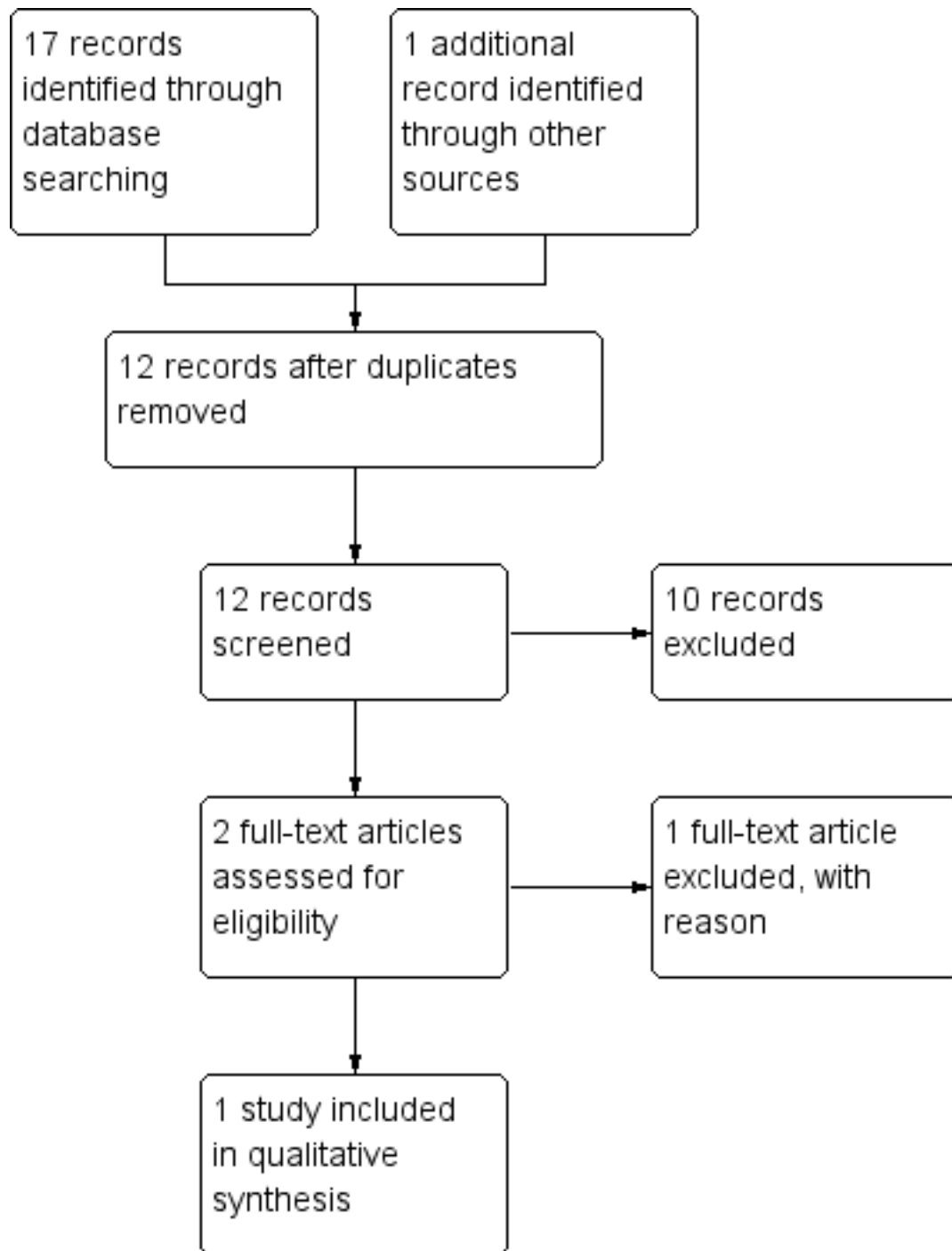
Description of studies

Results of the search

The Cochrane Central Register of Controlled Trials (CENTRAL) search yielded 2 studies; the MEDLINE search, another 2 studies; and the EMBASE search, 13 studies. We checked the reference lists and handsearched journals and congress abstracts, identifying one additional potentially relevant study. We did not identify any ongoing trials.

After excluding non-relevant and duplicated records, we retrieved two possibly eligible randomised controlled trials (RCTs) for more detailed evaluation (Celebi 2006; Lundin 2014). Only one study met the review inclusion criteria (Lundin 2014). We excluded Celebi 2006 because it was conducted in women with cervical cancer. See study flow diagram ([Figure 1](#)).

Figure 1. Study flow diagram.



Included studies

We found one RCT that met the inclusion criteria ([Lundin 2014](#)) and present full details in '[Characteristics of included studies](#)'.

Study design and setting

The included study was a randomised double blind, placebo-controlled multicentre study that took place in two university hospitals and two central hospitals in the southeast health region of Sweden between March 2008 and May 2012.

Participants

The included study recruited 100 participants with clinically advanced ovarian cancer scheduled for cytoreductive surgery who complied with inclusion and exclusion criteria. Fifty participants were randomly allocated to receive tranexamic acid and 50 to receive placebo. Inclusion criteria were as follows: women 18 years of age or over; having an American Society of Anesthesiologists score of less than 3 and speaking Swedish fluently. Exclusion criteria were: allergic to tranexamic acid; receiving anticoagulants within the past month; having past or current laboratory results suggesting bleeding disorders, coagulopathy or thromboembolic events; having a history of myocardial infarction within the last year; presenting with unstable angina or severe coronary disease; having reduced renal function, and diagnosed with severe psychiatric or mental disorders.

Sample size

The trial authors considered a 500 mL reduction in total blood loss and a reduction in the requirement for RBC transfusions from 37% to 10% to be a clinical meaningful threshold, and they calculated the need for a sample size of 100 participants to demonstrate a difference at a 5% significance level (two-sided test) with an 80% power and an expected dropout rate of 25%.

Intervention

In the included study, participants assigned to the intervention arm received a single dose of tranexamic acid (15 mg/kg body weight, 100 mg/mL tranexamic acid) intravenously before the start of surgery. Those in the placebo arm received an identical package containing normal saline (0.9% NaCl) by the same method.

Compliance and follow-up

Investigators collected complete data on perioperative clinical characteristics, outcomes of blood loss and transfusion for all participants. At the five-week follow-up visit, seven participants (two (4%) in the tranexamic acid group and five (10%) in the placebo group) were lost to follow-up. However, only 56 participants (56%) in both arms (26 or 52% in the tranexamic acid group and 30 or 60% in the placebo group) underwent lower extremity duplex ultrasound examination to evaluate venous thrombosis at five weeks.

Outcomes

Primary endpoints were the total amount of perioperative blood loss and the rate of red blood cell (RBC) transfusion. Secondary endpoints were the incidences of readmission, reoperation and thromboembolic events. Investigators performed analyses according to intention-to-treat principles.

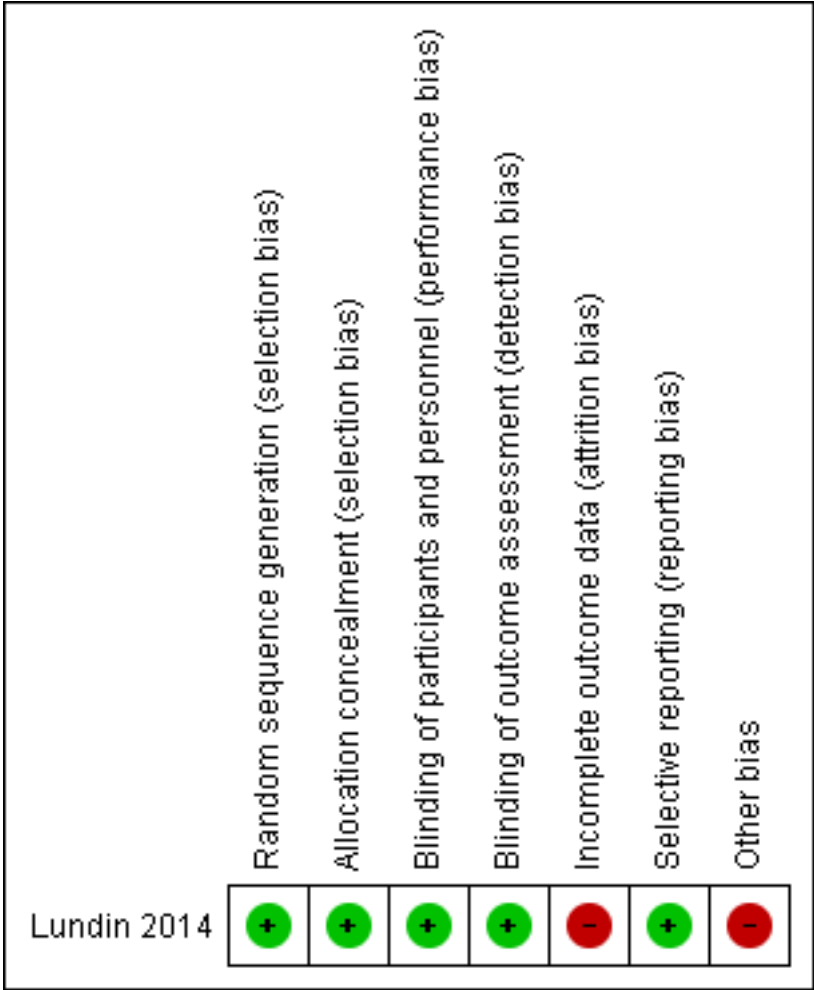
Excluded studies

Of the two potentially eligible studies that we assessed in full-text form ([Lundin 2014](#); [Celebi 2006](#)), we excluded one because it was conducted in women who had undergone type III hysterectomy for cervical cancer; the trial did not recruit any women with advanced ovarian cancer ([Celebi 2006](#)). See '[Characteristics of excluded studies](#)'.

Risk of bias in included studies

Overall, [Lundin 2014](#) was at low risk of bias, since it satisfied five criteria used to determine risk of bias; (see [Figure 2](#)).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The trial used stratified randomisation to balance allocations among the four participating centres. Each individual assignment from the computer-generated sequence was numbered sequentially. We confirmed via personal correspondence that allocation concealment was adequate. Overall, we deemed this domain to have a low risk of bias (Figure 2).

Blinding

The authors of the included study stated that all hospital staff and participants involved in the included study were blinded to the treatment assigned (verified by personal correspondence). The local hospital pharmacy prepared the study medications containing

either tranexamic acid or saline (0.9% NaCl) as placebo with the same appearance and packaging. We determined this to indicate low risk of bias (Figure 2).

Incomplete outcome data

After randomisation, 50 participants were assigned to receive a single dose of tranexamic acid (15 mg/kg body weight) and the remaining 50 to receive placebo. Investigators collected complete data on perioperative clinical characteristics, outcomes of blood loss and transfusion from all participants. In addition, at the five-week follow-up visit, only seven participants in both arms (two (4%) in the tranexamic acid group and five (10%) in the placebo group) were lost to follow-up. However, only 56 participants

(56%) in both arms had undergone lower extremity duplex ultrasound examination to evaluate lower extremity venous thrombosis (26 (52%) in the tranexamic acid group and 30 (60%) in the placebo group). As the protocol stated that incidence of thromboembolic events was one of the outcomes of interest, we therefore determined this domain to be at high risk of bias (Figure 2).

Selective reporting

Primary endpoints of the included study consisted of the amount of perioperative blood loss and the rate of red blood cell (RBC) transfusion. Secondary endpoints were the incidence of readmission, reoperation, infection and thromboembolic events. The trial did report all of these outcomes, so we judged this domain to be at a low risk of bias (Figure 2).

Other potential sources of bias

There were baseline imbalances in preoperative clinical characteristics between the two comparison groups with regard to the stage distribution of EOC and the types of surgical procedure carried out. In addition, the included study had no well-defined criteria or protocol for transfusion of blood components. We determined this to confer a high risk of other bias because these parameters are likely to have a significant impact on the outcomes of interest (Figure 2).

Effects of interventions

See: [Summary of findings for the main comparison](#)

We found only one study in 100 women that met our inclusion criteria, reporting perioperative blood loss and the rate of blood component transfusion (Lundin 2014).

Primary outcome

Tranexamic acid given preoperatively was associated with a reduction in blood loss compared to placebo. Means of total blood loss were 668.34 mL and 916.93 mL (520 mL and 730 mL median values) for participants assigned to the tranexamic acid and placebo groups, respectively. However, this difference did not constitute a clinically important benefit (mean difference (MD) – 248.59; 95% CI, – 550.9 to 53.79). We judged the quality of the evidence on this issue as low. See [Table 1](#), [Summary of findings for the main comparison](#), [Analysis 1.1](#),

Secondary outcomes

Number of transfused units of blood components

Compared to participants in the placebo group, the total number of transfused units of red blood cells (RBC) was lower in the participants receiving preoperative tranexamic acid (18 units versus

53 units). The mean number of transfused units of RBC among women allocated to the tranexamic acid and placebo groups were 0.76 and 1.06 units, respectively. This difference did not reach the threshold for clinically important effect (MD – 0.30; 95% CI, – 0.09 to 0.28). The mean number of transfused units of plasma was also lower in women enrolled to the tranexamic acid group compared to those in the placebo group. Again, this difference was not clinically important (MD – 0.12, 95% CI, – 0.41 to 0.17). We judged the quality of the evidence on this issue to be low. See [Table 1](#); [Summary of findings for the main comparison](#); [Analysis 2.1](#); [Analysis 2.2](#).

Rate of RBC transfusion

See '[Differences between protocol and review](#)'.

Although tranexamic acid did not confer a clinically important benefit on the need for RBC transfusion, the rate of RBC transfusion was lower in women receiving tranexamic acid (22% versus 30%, respectively; RR, 0.68; 95% CI, 0.40 to 1.15). We judged the quality of the evidence on the effect of tranexamic acid on the need for blood transfusion as low (see [Table 1](#); [Summary of findings for the main comparison](#); [Analysis 3.1](#)).

Rate of plasma transfusion

(see [Differences between protocol and review](#))

Women assigned to the tranexamic acid group had a lower rate of plasma transfusion compared to those in the placebo group (8% versus 18%, respectively) ([Table 1](#)). However, this difference was not clinically important (RR, 0.44; 95% CI, 0.15 to 1.35; low quality evidence, see [Summary of findings for the main comparison](#); [Analysis 3.2](#)).

Incidence of reoperation

The incidence of reoperation in women receiving prophylactic tranexamic acid was 10%, which was comparable to the 12% reported for women in the placebo arm (RR, 0.83; 95% CI, 0.27 to 2.55; very low quality evidence, see [Table 1](#); [Summary of findings for the main comparison](#); [Analysis 4.1](#)).

Incidence of readmission

Women receiving prophylactic tranexamic acid had a higher incidence of readmission compared to those who were assigned to placebo group (22% versus 8%, respectively; [Table 1](#)). However, this difference was not clinically important (RR, 2.75; 95% CI 0.94 to 8.06; very low quality evidence, see [Summary of findings for the main comparison](#); [Analysis 5.1](#)).

Incidence of venous thromboembolic events

Two participants assigned to tranexamic acid group developed either superficial ($n = 1$) or deep venous thrombosis ($n = 1$) in the leg, while four participants receiving placebo experienced muscle vein thrombosis ($n = 3$) or deep vein thrombosis ($n = 1$) in the leg (Table 1). This difference did not reach a clinically important effect (RR, 0.50; 95% CI, 0.10 to 2.61; very low quality evidence, see [Summary of findings for the main comparison](#); Analysis 6.1).

Incidence of arterial thromboembolic events

Arterial thromboembolic events were rare (Table 1). Only one participant assigned to the placebo group experienced arterial thrombosis in the popliteal artery. No participants in the intervention group developed arterial thromboembolic events (RR, 0.33, 95% CI, 0.01 to 7.99) (very low quality evidence, see [Summary of findings for the main comparison](#); Analysis 6.2).

The included trial did not report other secondary outcomes (see [Differences between protocol and review](#)).

DISCUSSION

Summary of main results

In the single included study, there were no clinically important differences between women receiving tranexamic acid and those receiving a placebo in terms of mean total estimated blood loss and mean number of transfused units of blood components. The number of adverse events, including incidence of reoperation, readmission and thromboembolic events, did not differ between the two comparison groups (see [Summary of findings for the main comparison](#)).

Overall completeness and applicability of evidence

This review included one RCT evaluating preoperative tranexamic acid in 100 women with clinically advanced EOC in Sweden. The intervention that was evaluated in the included study was the same one that this review aims to address. Primary outcomes were blood loss and the blood transfusion rate. Secondary outcomes included RBC transfusion, reoperation, readmission and thromboembolic events. Due to incomplete data and limited evidence obtained from a single RCT, we consider that the evidence for the effectiveness and safety of tranexamic acid in reducing blood loss during cytoreductive surgery for advanced ovarian cancer is inconclusive. The study included in the review took place in a developed country, and experienced gynaecologic oncologists carried out all operations. Therefore, generalisation of the results to different settings might be limited.

Quality of the evidence

The greatest threat to the validity of the included study is likely to be the risk of bias, since the study had no well-defined criteria or protocol for transfusion of blood components. Thus, the rate of blood transfusion may vary depending on the practice of each participating centre. In addition, only 56% of participants in both arms underwent lower extremity duplex ultrasound examination to evaluate lower extremity venous thrombosis. The other potential bias was the imbalance of baseline clinical characteristics between the two comparison groups in the included study, particularly with regard to the stage distribution of EOC and the types of surgical procedure carried out, which were likely to have had an impact on the outcomes of interest.

We assessed the quality of evidence using the GRADE approach for each outcome. Based on the concerns regarding the risk of the potential bias and imprecision, we downgraded the evidence to low quality for the amount of estimated blood loss, number of transfused units of blood components and rate of blood component transfusion. We downgraded the evidence to very low quality for adverse events due to sparseness of data. Overall, we determined that the evidence for the effectiveness and safety of a single dose tranexamic acid given immediately prior to surgery to reduce blood loss during cytoreduction for advanced ovarian cancer was inconclusive.

Potential biases in the review process

With support from the Cochrane Gynecological Cancer Group, the authors of this review carried out a comprehensive search, including a thorough search of the grey literature. Two review authors independently screened all potentially relevant studies and extracted data. The review authors also carefully assessed risk of bias in the included trial (Figure 2). We restricted studies to RCTs, as they provide the best evidence. However, as there was only one study that met the review inclusion criteria, we cannot definitively rule out the possibility of publication bias. None of the review authors have any links to drug companies or a financial interest in the prescription of the drug under assessment, nor were they involved in the conduct of the included study. Thus, there were no issues related to bias due to conflicts of interests in this review.

Agreements and disagreements with other studies or reviews

We are not aware of any studies or reviews that have determined the effectiveness and safety of tranexamic acid given perioperatively with the aim of reducing haemorrhage during cytoreductive surgery for advanced ovarian cancer.

Tranexamic acid given perioperatively has proven to be an effective intervention in reducing blood loss and the need for allogeneic blood transfusion in a number of Cochrane systematic reviews

in a variety of surgical settings (acute trauma, Roberts 2015; urgent and emergency surgery, Perel 2013) and in different patient groups (pregnant women giving birth, Novikova 2015; women with uterine fibroids undergoing myomectomy, Kongnyuy 2014). This review, which identified only one RCT that met the review inclusion criteria, found that participants assigned to tranexamic acid tended to have lower volume of estimated total blood loss and a lower rate of blood transfusion requirement. However, the difference in volume of blood loss was low (median difference of 210 mL) and did not lead to a difference in the need for blood transfusion, suggesting the treatment did not confer a clinically meaningful benefit (see [Summary of findings for the main comparison](#)). Findings of this review should be considered with caution. Firstly, the mean reduction in estimated total blood loss and the decrease in the rate of RBC transfusion (250 mL, and 14%, respectively) were far lower than originally expected. Trial investigators set a sample size to detect a 500 mL reduction in total amount of blood loss and a 20% reduction in the requirement for RBC transfusion. Given the low power of the included study, we cannot rule out a smaller magnitude of reduction in estimated amount of blood loss and rate of RBC transfusion of tranexamic acid than those set out in the included study.

Secondly, people with cancer commonly have bleeding tendencies arising from various cancer-specific conditions, either due to localised bleeding from local tumour invasion or as systemic bleeding secondary to loss of haemostatic factors in enlarged extravascular space, hypoproteinaemia, reduced synthesis of coagulation factors, platelet dysfunctions or increased fibrinolysis (Kvolik 2010). Studies have reported associations between ovarian cancer and several enhanced fibrinolysis as a result of elevated levels of D-dimer and other fibrin degradation products (FDPs), and decreased antithrombin III levels (Gadducci 1994; Koh 2006; Sitalakshmi 2008). These abnormal coagulation parameters appear to be more pronounced in people with an advanced stage of disease (Koh 2006; Sitalakshmi 2008). Based on these findings, women with advanced ovarian cancer may be at an increased risk of excessive bleeding during surgery compared to people in other surgical settings. A smaller magnitude of effect of tranexamic acid in lowering blood loss in women with advanced ovarian cancer undergoing cytoreductive surgery could therefore be expected. As currently limited data are available from just one study, further well-designed RCTs with adequate study power are warranted.

AUTHORS' CONCLUSIONS

Implications for practice

The limited evidence obtained from a single RCT presented in this review suggests that the beneficial effects of a single dose tranexamic acid given before cytoreductive surgery for advanced ovarian cancer did not reach a clinically important level. In addition, evidence for the safety of tranexamic acid used in this surgical setting is inconclusive due to a small number of tranexamic acid-related adverse events and incomplete data collection. At present the evidence does not support the routine administration of tranexamic acid in women undergoing cytoreductive surgery for advanced ovarian cancer.

Implications for research

There is a need for an adequately sized, placebo-controlled trial with a well-defined protocol for blood transfusion and a protocol for evaluating tranexamic acid-related adverse events to shed more light on the effectiveness of tranexamic acid given perioperatively to reduce blood loss during cytoreductive surgery for advanced ovarian cancer.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Lundin 2014

Methods	A randomised double blind, placebo-controlled multicentre study conducted in 2 university hospitals and 2 central hospitals in the southeast health region of Sweden Study duration: March 2008 to May 2012
Participants	100 women with presumed advanced EOC scheduled for cytoreductive surgery and complying with inclusion/exclusion criteria; 50 were randomly allocated to receive tranexamic acid and 50 to receive placebo. Median age of participants in tranexamic acid and those in placebo groups were 63 years and 64.5 years, respectively. Approximately 20.5% and 7.5% of participants assigned to tranexamic acid and placebo groups, respectively, had stage IV ovarian cancer. Approximately 22% and 12% of participants in tranexamic acid and placebo groups, respectively, underwent retroperitoneal lymphadenectomy Inclusion criteria: women ≥ 18 years of age with an American Society of Anesthesiologists score of ≤ 3 ; fluent in Swedish Exclusion criteria: allergy to tranexamic acid; received anticoagulants within the past month; with previous or current laboratory results suggesting bleeding disorders, coagulopathy or thromboembolic events; a history of myocardial infarction within the last year; presenting with unstable angina or severe coronary disease; reduced renal function; severe psychiatric or mental disorder
Interventions	Intervention arm: participants received a single dose of tranexamic acid (15 mg/kg body weight, 100 mg/mL tranexamic acid) immediately before the start of surgery Control arm: participants received the same volume of normal saline (0.9% NaCl) prepared in identical packaging and given in the same fashion
Outcomes	Primary endpoints: amount of blood loss and rate of red blood cell (RBC) transfusion Secondary endpoints: readmission, reoperation, and thromboembolic events. Data regarding amount of blood loss and rate of RBC transfusion were collected after operation. At the 5-week postoperative visit, participants were interviewed about postoperative complications and underwent lower extremity duplex ultrasound for evaluating venous thrombosis regardless of symptoms
Notes	The included study had no well-defined criteria or protocol for transfusion of blood components. The authors of the included study broadly stated that "perioperative bleeding was managed according to clinical practice and blood transfusion was usually given when the haemoglobin level measured during the surgery or postoperatively was below 90 g/L" and "postoperative blood transfusion was given according to the patient's clinical well being and haemoglobin level." In addition, participants were optionally referred to lower extremity duplex ultrasound to look for venous thrombosis regardless of symptoms at the time of 5-week follow-up visit Imbalance of participant allocation was observed. Relative to participants assigned to placebo group, a higher proportion of participants receiving tranexamic acid were diagnosed with stage IV ovarian cancer (20.5% versus 7.5%), had undergone extensive surgery (82% versus 70%) and were overweight or obese (62% versus 38%)

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was stratified according to each individual centre among the four centres participating in the trial. Each individual assignment from the computer-generated sequences was numbered sequentially
Allocation concealment (selection bias)	Low risk	Trial authors confirmed adequate allocation concealment by correspondence
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Hospital staff and participants involving in this trial were blinded to the treatment assigned. The local hospital pharmacy prepared the study medications containing either tranexamic acid or saline (0.9% NaCl) as placebo with the same appearance and packaging
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded to treatment allocation (data additionally provided by the trial authors)
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 56 participants (56%) in both arms underwent lower extremity duplex ultrasound examination to evaluate lower extremity venous thrombosis (26 or 52% in the tranexamic acid group and 30 or 60% in the placebo group)
Selective reporting (reporting bias)	Low risk	All potential relevant outcomes were reported.
Other bias	High risk	There were several imbalances in baseline preoperative clinical characteristics between the two groups, including participants' body mass index, the distribution of stage of disease and types of surgical procedure carried out. In addition, the included trial had no well-defined criteria or protocol for transfusion of blood components. Thus, the rate of blood transfusion may vary depending on the practice of each participating centre

EOC: epithelial ovarian cancer.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Celebi 2006	This randomised study, entitled “The role of antifibrinolytic agents in gynaecologic cancer surgery” was conducted to determine the effectiveness of crystalloid and colloid solutions, tranexamic acid, and epsilon-aminocaproic acid for reducing the need for allogenic blood transfusion and for coagulation and fibrinolysis. This trial randomly assigned 105 participants into 4 groups, receiving: crystalloid solution, colloid solution, 10 mg/kg of tranexamic acid, or 100 mg/kg of epsilon-aminocaproic acid. The reason for exclusion was that it was carried out solely in women who had undergone type 3 hysterectomy for early stage cervical cancer. The study recruited no women with advanced ovarian cancer

DATA AND ANALYSES

Comparison 1. Estimated total blood loss (mL)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Estimated total blood loss (mL)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Comparison 2. Number of transfused units of blood components

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of transfused units of RBC	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2 Number of transfused units of plasma	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Comparison 3. Rate of blood component transfusion

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Red blood cell transfused women	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2 Plasma transfused women	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Comparison 4. Incidence of reoperation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Reoperation	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Comparison 5. Incidence of readmission

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Readmission	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Comparison 6. Incidence of thromboembolic events

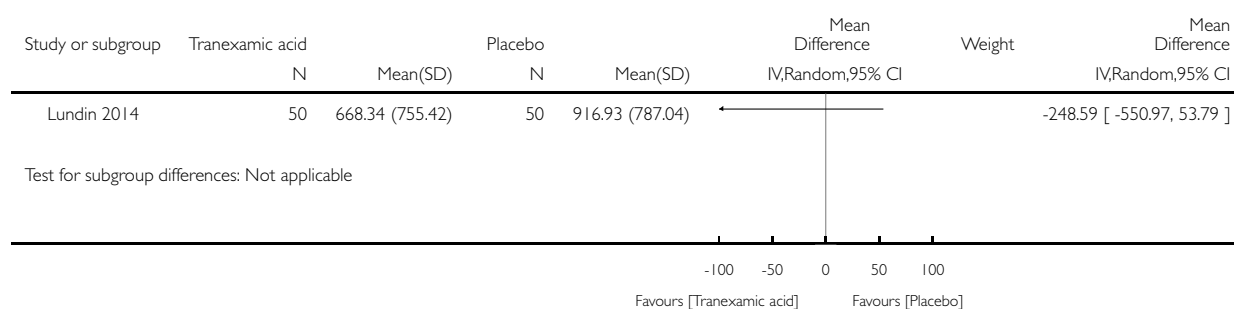
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Venous thromboembolic events	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2 Arterial thromboembolic events	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 Estimated total blood loss (mL), Outcome 1 Estimated total blood loss (mL).

Review: Effectiveness of tranexamic acid in reducing blood loss during cytoreductive surgery for advanced ovarian cancer

Comparison: 1 Estimated total blood loss (mL)

Outcome: 1 Estimated total blood loss (mL)

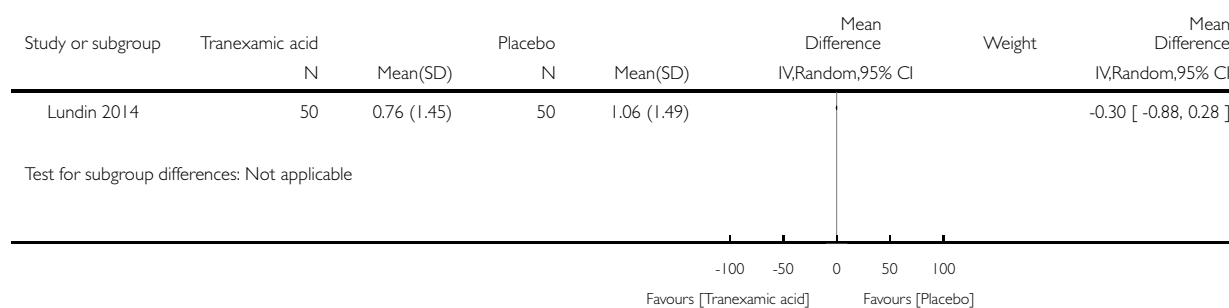


Analysis 2.1. Comparison 2 Number of transfused units of blood components, Outcome 1 Number of transfused units of RBC.

Review: Effectiveness of tranexamic acid in reducing blood loss during cytoreductive surgery for advanced ovarian cancer

Comparison: 2 Number of transfused units of blood components

Outcome: 1 Number of transfused units of RBC

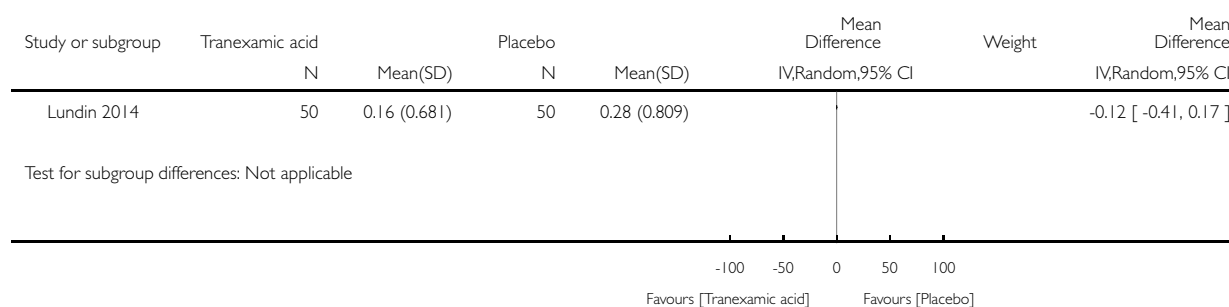


Analysis 2.2. Comparison 2 Number of transfused units of blood components, Outcome 2 Number of transfused units of plasma.

Review: Effectiveness of tranexamic acid in reducing blood loss during cytoreductive surgery for advanced ovarian cancer

Comparison: 2 Number of transfused units of blood components

Outcome: 2 Number of transfused units of plasma

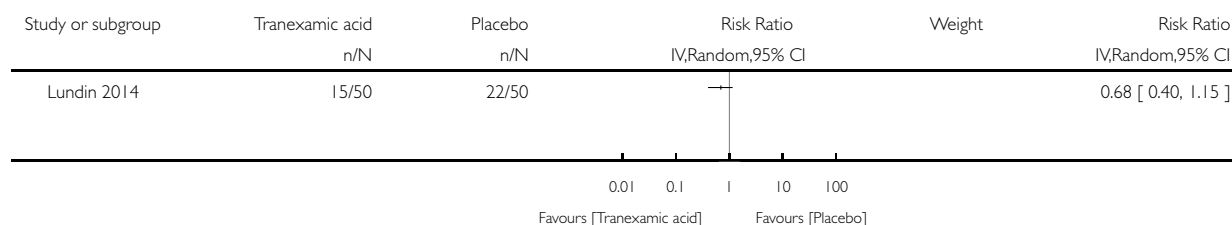


Analysis 3.1. Comparison 3 Rate of blood component transfusion, Outcome 1 Red blood cell transfused women.

Review: Effectiveness of tranexamic acid in reducing blood loss during cytoreductive surgery for advanced ovarian cancer

Comparison: 3 Rate of blood component transfusion

Outcome: 1 Red blood cell transfused women

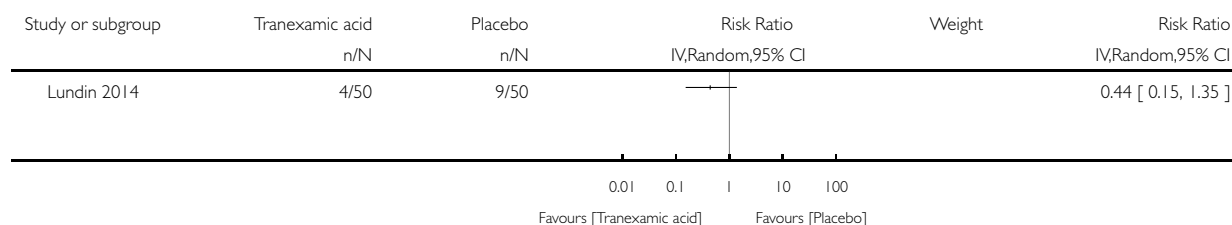


Analysis 3.2. Comparison 3 Rate of blood component transfusion, Outcome 2 Plasma transfused women.

Review: Effectiveness of tranexamic acid in reducing blood loss during cytoreductive surgery for advanced ovarian cancer

Comparison: 3 Rate of blood component transfusion

Outcome: 2 Plasma transfused women

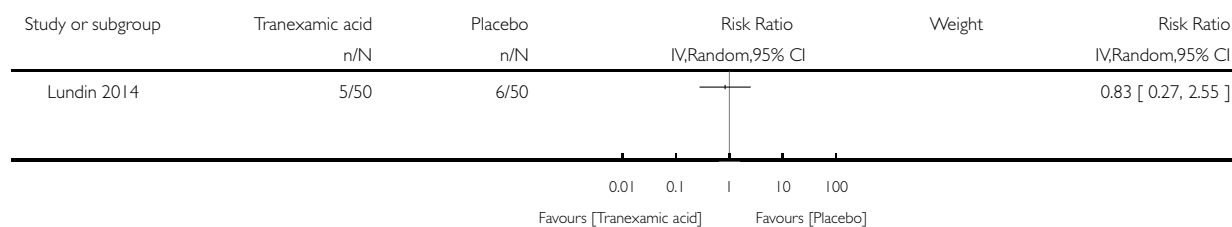


Analysis 4.1. Comparison 4 Incidence of reoperation, Outcome 1 Reoperation.

Review: Effectiveness of tranexamic acid in reducing blood loss during cytoreductive surgery for advanced ovarian cancer

Comparison: 4 Incidence of reoperation

Outcome: 1 Reoperation

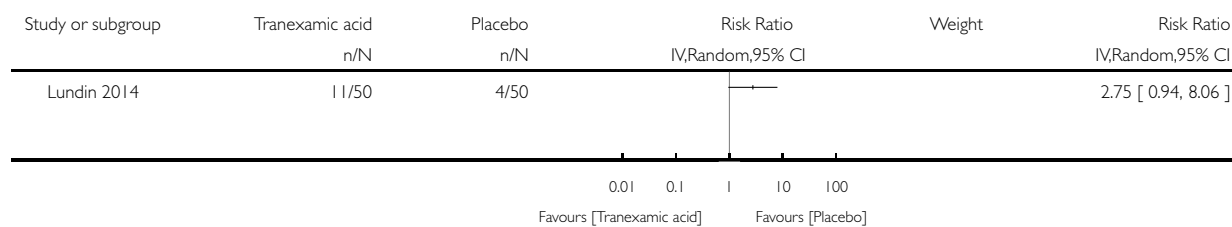


Analysis 5.1. Comparison 5 Incidence of readmission, Outcome 1 Readmission.

Review: Effectiveness of tranexamic acid in reducing blood loss during cytoreductive surgery for advanced ovarian cancer

Comparison: 5 Incidence of readmission

Outcome: 1 Readmission

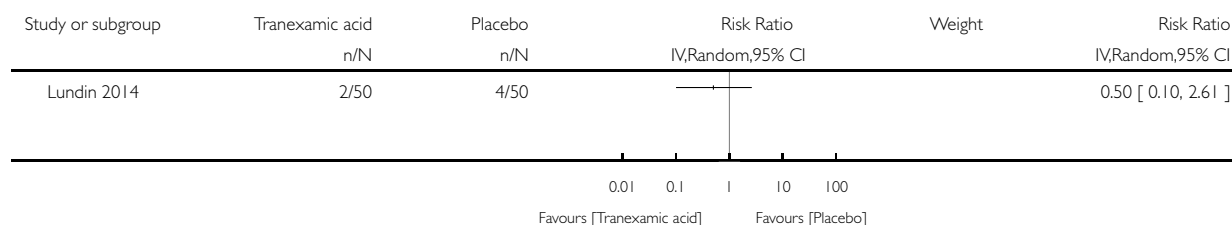


Analysis 6.1. Comparison 6 Incidence of thromboembolic events, Outcome 1 Venous thromboembolic events.

Review: Effectiveness of tranexamic acid in reducing blood loss during cytoreductive surgery for advanced ovarian cancer

Comparison: 6 Incidence of thromboembolic events

Outcome: 1 Venous thromboembolic events

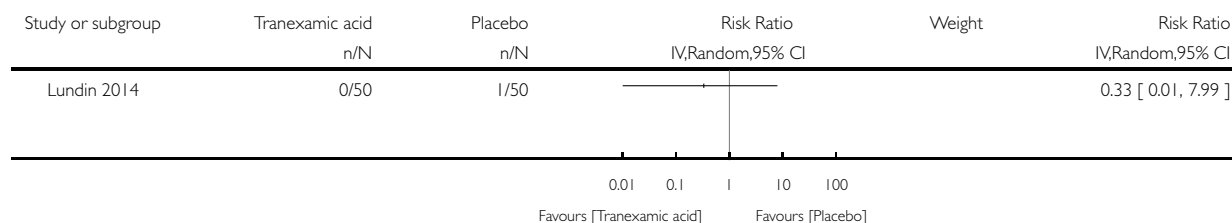


Analysis 6.2. Comparison 6 Incidence of thromboembolic events, Outcome 2 Arterial thromboembolic events.

Review: Effectiveness of tranexamic acid in reducing blood loss during cytoreductive surgery for advanced ovarian cancer

Comparison: 6 Incidence of thromboembolic events

Outcome: 2 Arterial thromboembolic events



ADDITIONAL TABLES

Table 1. Extracted data

Extracted data ^a	Tranexamic acid group (n = 50)	Placebo (n = 50)
Median total blood loss (mL), IQR	520, 211 to 870 ^b	730, 411 to 1278 ^b
Mean total blood loss (mL), SD	668, 755 ^b	916, 787 ^b
Mean number of units of transfused RBC, SD	0.76, 1.45 ^b	1.06, 1.49 ^b
Mean number of units of transfused plasma, SD	0.16, 0.68 ^b	0.28, 0.81 ^b
Number of RBC transfused participants	15 (30%)	22 (44%)
Number of plasma transfused participants	4 (8%)	9 (18%)
Number of participants who experienced reoperation	5 (10%)	6 (12%)
Number of participants who had to be readmitted	11 (22%)	4 (8%)
Number of participants who developed venous thromboembolic events	1 (2%)	4 (8%)
Number of participants who developed arterial thromboembolic events	1 (2%)	1 (2%)

IQR: interquartile range; **RBC:** red blood cell; **SD:** standard deviation.

^aData extracted from only one available randomised trial.

^bAdditional data provided by the trial authors ([Kjølhed 2015 \[pers comm\]](#)).

APPENDICES

Appendix I. 2014 the International Federation of Gynecology and Obstetrics (FIGO) ovarian cancer staging system

Stage	Findings
I	Tumor confined to ovaries
IA	Tumor limited to one ovary (capsule intact), no tumor on ovarian surface, no malignancy cells in the ascites or peritoneal washings
IB	Tumor limited to both ovaries (capsule intact), no tumor on ovarian surface, no malignancy cells in the ascites or peritoneal washings
IC	Tumor limited to one or both ovaries with any of the following: surgical spill intraoperatively, capsule rupture before surgery or tumor on ovarian surface, or malignancy cells present in the ascites or peritoneal washings
II	Tumor involves one or both ovaries with pelvic extension
IIA	Extension and/or implants on the uterus and/or fallopian tubes
IIB	Extension to other pelvic intraperitoneal tissues
III	Tumor involves one or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal nodes
IIIA	Metastasis to the retroperitoneal lymph nodes with or without microscopic peritoneal involvement beyond the pelvis
IIIB	Macroscopic peritoneal metastases beyond the pelvic brim ≤ 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
IIIC	Macroscopic peritoneal metastases beyond the pelvic brim >2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
IV	Distant metastasis excluding peritoneal metastases
IVA	Pleural effusion with positive cytology
IVB	Metastases to extra-abdominal organs or parenchymal metastases

Appendix 2. CENTRAL search strategy

- #1 MeSH descriptor: [Ovarian Neoplasms] explode all trees
- #2 ovar* near/5 (cancer* or tumor* or tumour* or neoplasm* or carcinoma* or adenocarcinoma* or malignan*)
- #3 #1 or #2
- #4 Any MeSH descriptor with qualifier(s): [Surgery - SU]
- #5 MeSH descriptor: [Gynecologic Surgical Procedures] explode all trees
- #6 cytoreduct* or debulk*
- #7 #4 or #5 or #6
- #8 MeSH descriptor: [Tranexamic Acid] this term only
- #9 tranexamic acid or amchafibrin or anvitoff or cyclokapron or cyklokapron or exacyl or kabi 2161 or lysteda or spotof or t-amcha or tranhexamic acid or transamin or ugurol or xp12b
- #10 #8 or #9
- #11 #3 and #7 and #10

Appendix 3. MEDLINE Ovid search strategy

- 1. exp Ovarian Neoplasms/
 - 2. (ovar* adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*)).mp.
 - 3. 1 or 2
 - 4. surgery.fs.
 - 5. exp Gynecologic Surgical Procedures/
 - 6. (cytoreduct* or debulk*).mp.
 - 7. 4 or 5 or 6
 - 8. Tranexamic Acid/
 - 9. (tranexamic acid or amchafibrin or anvitoff or cyclokapron or cyklokapron or exacyl or kabi 2161 or lysteda or spotof or t-amcha or tranhexamic acid or transamin or ugurol or xp12b).mp
 - 10. 8 or 9
 - 11. 3 and 7 and 10
- key: mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier
- fs= floating subheading

Appendix 4. EMBASE search strategy

- 1. exp ovary tumor/-
 - 2. (ovar* adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*)).mp.
 - 3. 1 or 2
 - 4. su.fs.
 - 5. exp gynecologic surgery/
 - 6. (cytoreduct* or debulk*).mp
 - 7. 4 or 5 or 6
 - 8. tranexamic acid/
 - 9. (tranexamic acid or amchafibrin or anvitoff or cyclokapron or cyklokapron or exacyl or kabi 2161 or lysteda or spotof or t-amcha or tranhexamic acid or transamin or ugurol or xp12b).mp.
 - 10. 8 or 9
 - 11. 3 and 7 and 10
- Key: mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword

Appendix 5. Risk of bias assessment

Risk of bias assessment based on chapter 8 of [Higgins 2011](#):

- Random sequence generation
 - i) Low risk of bias e.g. participants assigned to treatments on the basis of a computer-generated random sequence or a table of random numbers
 - ii) High risk of bias e.g. participants assigned to treatments on the basis of date of birth, clinic id-number or surname, or no attempt to randomise participants
 - iii) Unclear risk of bias e.g. not reported, information not available
- Allocation concealment
 - i) Low risk of bias e.g. where the allocation sequence could not be foretold
 - ii) High risk of bias e.g. allocation sequence could be foretold by patients, investigators or treatment providers
 - iii) Unclear risk of bias e.g. not reported.
- Blinding of participants and personnel
 - i) Low risk of bias if participants and personnel were adequately blinded
 - ii) High risk of bias if participants were not blinded to the intervention that the participant received
 - iii) Unclear risk of bias if this was not reported or unclear
- Blinding of outcomes assessors
 - i) Low risk of bias if outcome assessors were adequately blinded
 - ii) High risk of bias if outcome assessors were not blinded to the intervention that the participant received
 - iii) Unclear risk of bias if this was not reported or is unclear
- Incomplete outcome data: we will record the proportion of participants whose outcomes were not reported at the end of the study. We will code a satisfactory level of loss to follow-up for each outcome as:
 - i) Low risk of bias e.g. if fewer than 20% of participants were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms
 - ii) High risk of bias e.g. if more than 20% of participants were lost to follow-up or reasons for loss to follow-up differed between treatment arms
 - iii) Unclear risk of bias e.g. if loss to follow-up was not reported
- Selective reporting of outcomes
 - i) Low risk of bias e.g. review reports all outcomes specified in the protocol
 - ii) High risk of bias e.g. the study is suspected that outcomes have been selectively reported
 - iii) Unclear risk of bias e.g. it is unclear whether outcomes have been selectively reported
- Other bias
 - i) Low risk of bias e.g. the review authors do not suspect any other source of bias and the trial appears to be methodologically sound
 - ii) High risk of bias e.g. the review authors suspect that the trial was prone to an additional bias
 - iii) Unclear risk of bias e.g. the review authors are uncertain whether an additional bias may have been present

WHAT'S NEW

Last assessed as up-to-date: 31 May 2015.

Date	Event	Description
21 September 2016	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

CK conceived the review question, developed, coordinated and completed the review.

AM developed and completed the draft of the review.

ML performed part of the editing of the review and advised on part of the review.

PL developed and coordinated the development of the review, edited the review, and advised on the review.

All authors approved the final version of the review prior to submission.

DECLARATIONS OF INTEREST

Chumnan Kietpeerakool: none known.

Amornrat Supoken: none known.

Malinee Laopaiboon: none known.

Pisake Lumbiganon: none known.

SOURCES OF SUPPORT

Internal sources

- Department of Obstetrics and Gynaecology, Faculty of Medicine, Khon Kaen University, Thailand.
- Department of Biostatistics and Demography, Faculty of Public Health, Khon Kaen University, Khon Kaen, Thailand.
- Thai Cochrane Network of The Australasian Cochrane Centre, Thailand.

External sources

- Thailand Research Fund (Distinguished Professor Awards), Thailand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Type of outcome measures

The included study did not report several outcomes of interest stated in the review protocol, including length of surgery, length of hospital stay, postoperative haemoglobin, incidence of nausea/vomiting/diarrhoea and incidence of neurological adverse events.

We added two new secondary outcomes that reflect the amount of blood loss: rate of red blood cell transfusion (number of participants who required at least one unit of red blood cell transfusion) and rate of plasma transfusion (number of participants who required at least one unit of plasma transfusion).

Searches

In the protocol, we stated: “If ongoing trials that have not been published are identified through these searches, we plan to approach the principal investigators, and major co-operative groups active in this area, to ask for relevant data” However, we did not find any relevant ongoing trials or particularly active trial groups, so we did not make these contacts.

In the review, we added the lists of databases used for searching conference abstracts and proceedings (grey literature). We also added the WHO International Clinical Trial Registry (<http://apps.who.int/trialsearch/Default.aspx>) as a source of registers of clinical trials to be searched.

Considerations for future updates of the review

Data extraction and management

If a study with multiple intervention groups is identified, we intend to combine all relevant experimental intervention groups into a single group to create a single pair-wise comparison (Higgins 2011).

Assessment of risk of bias in included studies

When interpreting treatment effects and meta-analyses, we will take into account the risk of bias for the studies that contribute to that outcome. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the table.

Measure of treatment effect

Combining intervention groups to create a single pair-wise comparison, as stated in the protocol, was not necessary for this review since the included trial had only two comparison groups. However, we will take this step in future updates if appropriate.

Data collection and analysis

As there was only one trial that met our inclusion criteria, we were unable pool the results in meta-analyses, so it was not feasible to assess heterogeneity between the results of trials, reporting biases or conduct any subgroup or sensitivity analyses. In future update of this review, we will employ the following methods for data analysis.

Assessment of heterogeneity

We will assess clinical heterogeneity by considering the characteristics of the participants included in the studies. We will assess statistical heterogeneity in each meta-analysis using the τ^2 , I^2 and χ^2 statistic (Higgins 2003). We will regard heterogeneity as substantial if I^2 is greater than 50% and either τ^2 is greater than zero or the P value is less than 0.10 in the χ^2 test (Deeks 2001).

Assessment of reporting biases

We will construct funnel plots corresponding to meta-analyses of the primary outcome to assess the possibility of publication bias if we identify a sufficient number of included studies (i.e. more than 10). We will also carry out sensitivity analyses to investigate the effect on the pooled results if the funnel plots are asymmetrical (Sterne 2011).

Data synthesis

We will perform statistical analysis using RevMan 2014.

- For dichotomous outcomes, we intend to calculate the risk ratio for each study as well as for the pooled outcome.
- For continuous outcomes, we intend to pool the mean difference between the treatment arms if all trials measured the outcome on the same scale; otherwise we will pool the standardised mean differences.

We will use the random-effects model with inverse variance weighting for all meta-analyses if feasible (DerSimonian 1986). We will prepare a 'Summary of findings' table to present the results of the meta-analysis, based on the methods described in Chapter 11 of the

Cochrane Handbook for Systematic Reviews of Interventions (Schünemann 2011). We will present the results of the meta-analysis for the primary outcome and adverse events as outlined in the 'Types of outcome measures' section.

Subgroup analysis and investigation of heterogeneity

We will conduct subgroup analyses for the following factors if we identify substantial heterogeneity.

1. Route of administration of tranexamic acid (intravenous, oral or topical administration).
2. Dose of tranexamic acid (single dose versus multiple doses).
3. Largest preoperative tumour size, excluding ovarian mass (≤ 5 cm versus > 5 cm).

We will assess subgroup differences by interaction tests available within [RevMan 2014](#). We will report the results of subgroup analyses using the Chi^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We will perform a sensitivity analysis in order to determine the impact of the following factors.

1. Repeating the analysis excluding unpublished studies (if any).
2. Repeating the analysis excluding studies judged to be at high or unclear risk of bias for allocation concealment.

NOTES

Parts of the methods section of this protocol are based on a standard template established by the Cochrane Gynaecological, Neuro-oncology and Orphan Cancers Group.

INDEX TERMS

Medical Subject Headings (MeSH)

Antifibrinolytic Agents [*therapeutic use]; Blood Loss, Surgical [*prevention & control; statistics & numerical data]; Blood Transfusion [statistics & numerical data]; Cytoreduction Surgical Procedures [adverse effects; *methods]; Erythrocyte Transfusion [*statistics & numerical data]; Incidence; Ovarian Neoplasms [pathology; *surgery]; Patient Readmission [statistics & numerical data]; Plasma; Randomized Controlled Trials as Topic; Reoperation [statistics & numerical data]; Thromboembolism [epidemiology]; Tranexamic Acid [*therapeutic use]

MeSH check words

Adult; Female; Humans



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Antenatal breastfeeding education for increasing breastfeeding duration (Review)

Lumbiganon P, Martis R, Laopaiboon M, Festin MR, Ho JJ, Hakimi M

Lumbiganon P, Martis R, Laopaiboon M, Festin MR, Ho JJ, Hakimi M.
Antenatal breastfeeding education for increasing breastfeeding duration.
Cochrane Database of Systematic Reviews 2016, Issue 12. Art. No.: CD006425.
DOI: 10.1002/14651858.CD006425.pub4.

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	4
BACKGROUND	6
OBJECTIVES	7
METHODS	7
RESULTS	12
Figure 1.	14
Figure 2.	15
DISCUSSION	19
AUTHORS' CONCLUSIONS	20
ACKNOWLEDGEMENTS	21
REFERENCES	21
CHARACTERISTICS OF STUDIES	29
DATA AND ANALYSES	64
Analysis 1.1. Comparison 1 One type of BF education versus standard/routine care, Outcome 1 Duration of any breastfeeding.	68
Analysis 1.2. Comparison 1 One type of BF education versus standard/routine care, Outcome 2 Any breastfeeding at 3 months.	69
Analysis 1.3. Comparison 1 One type of BF education versus standard/routine care, Outcome 3 Any breastfeeding at 6 months.	70
Analysis 1.4. Comparison 1 One type of BF education versus standard/routine care, Outcome 4 Exclusive breastfeeding at 3 months.	71
Analysis 1.5. Comparison 1 One type of BF education versus standard/routine care, Outcome 5 Exclusive breastfeeding at 6 months.	72
Analysis 1.6. Comparison 1 One type of BF education versus standard/routine care, Outcome 6 Initiation of breastfeeding.	73
Analysis 1.7. Comparison 1 One type of BF education versus standard/routine care, Outcome 7 Initiation of BF (cluster-randomised trial).	74
Analysis 1.8. Comparison 1 One type of BF education versus standard/routine care, Outcome 8 Mastitis.	75
Analysis 1.9. Comparison 1 One type of BF education versus standard/routine care, Outcome 9 Breastfeeding complication (nipple pain).	76
Analysis 1.10. Comparison 1 One type of BF education versus standard/routine care, Outcome 10 Breastfeeding complication (nipple trauma).	76
Analysis 1.11. Comparison 1 One type of BF education versus standard/routine care, Outcome 11 Breastfeeding problems.	77
Analysis 2.1. Comparison 2 One type of BF education versus a different type of BF education, Outcome 1 Any breastfeeding at 3 months.	78
Analysis 2.2. Comparison 2 One type of BF education versus a different type of BF education, Outcome 2 Any breastfeeding at 6 months.	78
Analysis 2.3. Comparison 2 One type of BF education versus a different type of BF education, Outcome 3 Exclusive breastfeeding at 6 months.	79
Analysis 2.4. Comparison 2 One type of BF education versus a different type of BF education, Outcome 4 Initiation of BF	80
Analysis 3.1. Comparison 3 Multiple methods of BF education versus a single method of BF education, Outcome 1 Duration of any breastfeeding (days).	80
Analysis 3.2. Comparison 3 Multiple methods of BF education versus a single method of BF education, Outcome 2 Any breastfeeding at 6 months.	81
Analysis 4.1. Comparison 4 Different combinations of multiple methods of providing BF education, Outcome 1 Any breastfeeding at 4 months (cluster-randomised trial).	82

Analysis 4.2. Comparison 4 Different combinations of multiple methods of providing BF education, Outcome 2 Exclusive breastfeeding at 3 months.	83
Analysis 4.3. Comparison 4 Different combinations of multiple methods of providing BF education, Outcome 3 Exclusive breastfeeding at 6 months.	84
Analysis 5.1. Comparison 5 Multiple methods of BF education versus standard/routine care, Outcome 1 Duration of any breastfeeding (days).	84
Analysis 5.2. Comparison 5 Multiple methods of BF education versus standard/routine care, Outcome 2 Exclusive breastfeeding at 3 months.	85
Analysis 5.3. Comparison 5 Multiple methods of BF education versus standard/routine care, Outcome 3 Exclusive breastfeeding at six months.	86
Analysis 5.4. Comparison 5 Multiple methods of BF education versus standard/routine care, Outcome 4 Initiation of breastfeeding.	87
Analysis 6.1. Comparison 6 Summary of findings: one type of BF education versus standard/routine care, Outcome 1 Initiation of breastfeeding.	88
Analysis 6.2. Comparison 6 Summary of findings: one type of BF education versus standard/routine care, Outcome 2 Exclusive breastfeeding at 3 months.	89
Analysis 6.3. Comparison 6 Summary of findings: one type of BF education versus standard/routine care, Outcome 3 Exclusive breastfeeding at 6 months.	90
Analysis 6.4. Comparison 6 Summary of findings: one type of BF education versus standard/routine care, Outcome 4 Any breastfeeding at 3 months.	91
Analysis 6.5. Comparison 6 Summary of findings: one type of BF education versus standard/routine care, Outcome 5 Any breastfeeding at 6 months.	92
APPENDICES	92
WHAT'S NEW	93
HISTORY	93
CONTRIBUTIONS OF AUTHORS	94
DECLARATIONS OF INTEREST	94
SOURCES OF SUPPORT	94
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	94
INDEX TERMS	95

Antenatal breastfeeding education for increasing breastfeeding duration

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ABSTRACT

Background

Breast milk is well recognised as the best food source for infants. The impact of antenatal breastfeeding (BF) education on the duration of BF has not been evaluated.

Objectives

To assess the effectiveness of antenatal breastfeeding (BF) education for increasing BF initiation and duration.

Search methods

We searched Cochrane Pregnancy and Childbirth's Trials Register on 1 March 2016, CENTRAL (*The Cochrane Library*, 2016, Issue 3), MEDLINE (1966 to 1 March 2016) and Scopus (January 1985 to 1 March 2016). We contacted experts and searched reference lists of retrieved articles.

Selection criteria

All identified published, unpublished and ongoing randomised controlled trials (RCTs) assessing the effect of formal antenatal BF education or comparing two different methods of formal antenatal BF education, on the duration of BF. We included RCTs that only included antenatal interventions and excluded those that combined antenatal and intrapartum or postpartum BF education components. Cluster-randomised trials were included in this review. Quasi-randomised trials were not eligible for inclusion.

Data collection and analysis

We assessed all potential studies identified as a result of the search strategy. Two review authors extracted data from each included study using the agreed form and assessed risk of bias. We resolved discrepancies through discussion. We assessed the quality of the evidence using the GRADE approach.

Main results

This review update includes 24 studies (10,056 women). Twenty studies (9789 women) contribute data to analyses. Most studies took place in high-income countries such as the USA, UK, Canada and Australia. In the first five comparisons, we display the included trials according to type of intervention without pooling data. For the 'Summary of findings' we pooled data for a summary effect.

Five included studies were cluster-randomised trials: all of these adjusted data and reported adjustments as odds ratios (OR). We have analysed the data using the generic inverse variance method and presented results as odds ratios, because we were unable to derive a cluster-adjusted risk ratio from the published cluster-trial. We acknowledge that the use of odds ratio prevents the pooling of these cluster trials in our main analyses.

One method of BF education with standard (routine) care

There were no group differences for duration of any BF in days or weeks. There was no evidence that interventions improved the proportion of women with any BF or exclusive BF at three or six months. Single trials of different interventions were unable to show that education improved initiation of BF, apart from one small trial at high risk of attrition bias. Many trial results marginally favoured the intervention but had wide confidence intervals crossing the line of no effect. BF complications such as mastitis and other BF problems were similar in treatment arms in single trials reporting these outcomes.

Multiple methods of BF education versus standard care

For all trials included in this comparison we have presented the cluster-adjusted odds ratios as reported in trial publications. One three-arm study found the intervention of BF booklet plus video plus Lactation Consultant versus standard care improved the proportion of women exclusively BF at three months (OR 2.60, 95% CI 1.25 to 5.40; women = 159) and marginally at six months (OR 2.40, 95% CI 1.00 to 5.76; women = 175). For the same trial, an intervention arm without a lactation consultant but with the BF booklet and video did not have the same effect on proportion of women exclusively BF at three months (OR 1.80, 95% CI 0.80 to 4.05; women = 159) or six months (OR 0.90, 95% CI 0.30 to 2.70; women = 184). One study compared monthly BF sessions and weekly cell phone message versus standard care and reported improvements in the proportion of women exclusively BF at both three and six months (three months OR 1.80, 95% CI 1.10 to 2.95; women = 390; six months OR 2.40, 95% CI 1.40 to 4.11; women = 390). One study found monthly BF sessions and weekly cell phone messages improved initiation of BF over standard care (OR 2.61, 95% CI 1.61 to 4.24; women = 380).

BF education session versus standard care, pooled analyses for 'Summary of findings' (SoF)

This comparison does not include cluster-randomised trials reporting adjusted odds ratios. We did not downgrade any evidence for trials' lack of blinding; no trial had adequate blinding of staff and participants. The SoF table presents risk ratios for all outcomes analysed. For proportion of women exclusively BF there is no evidence that antenatal BF education improved BF at three months (RR 1.06, 95% CI 0.90 to 1.25; women = 822; studies = 3; moderate quality evidence) or at six months (RR 1.07, 95% CI 0.87 to 1.30; women = 2161; studies = 4; moderate quality evidence). For proportion of women with any BF there were no group differences in BF at three (average RR 0.98, 95% CI 0.82 to 1.18; women = 654; studies = 2; $I^2 = 60\%$; low-quality evidence) or six months (average RR 1.05, 95% CI 0.90 to 1.23; women = 1636; studies = 4; $I^2 = 61\%$; high-quality evidence). There was no evidence that antenatal BF education could improve initiation of BF (average RR 1.01, 95% CI 0.94 to 1.09; women = 3505; studies = 8; $I^2 = 69\%$; high-quality evidence). Where we downgraded evidence this was due to small sample size or wide confidence intervals crossing the line of no effect, or both.

There was insufficient data for subgroup analysis of mother's occupation or education.

Authors' conclusions

There was no conclusive evidence supporting any antenatal BF education for improving initiation of BF, proportion of women giving any BF or exclusively BF at three or six months or the duration of BF. There is an urgent need to conduct a high-quality, randomised controlled study to evaluate the effectiveness and adverse effects of antenatal BF education, especially in low- and middle-income countries. Evidence in this review is primarily relevant to high-income settings.

PLAIN LANGUAGE SUMMARY

Antenatal breastfeeding education for increasing breastfeeding duration

Antenatal breastfeeding education for increasing breastfeeding duration (Review)
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What is the issue?

Breastfeeding (BF) can improve the child's health, the mother's health and mother-infant bonding. BF infants have lower rates of stomach and breathing problems, fewer ear infections and better speech, vision and overall development of physical and mental skills. The World Health Organization recommends that infants should be exclusively breastfed from birth to six months and then breastfed alongside age-appropriate, complementary feeding for two years and beyond. Many women are unable to follow these recommendations, and we want to know how to help women to breastfeed.

Why is this important?

Antenatal BF education is teaching women about BF during pregnancy, before the baby arrives. One reason women are unable to breastfeed has to do with lack of education and knowledge about how to breastfeed. We believe that improving pregnant women's knowledge of BF may help them to breastfeed longer, but we are unsure what types of education are most helpful to women.

What evidence did we find?

We included 24 studies with 10,056 women in the review, and 20 studies involving 9789 women contributed data to the analyses. Most studies took place in high-income countries including the USA, Canada, UK and Australia. Peer counselling, lactation consultation and formal BF education during pregnancy do not appear to improve uptake of BF or duration. However, some larger trials in different settings (one in Nigeria and one in Singapore) had some evidence that education may help.

What does this mean?

We are still unsure if antenatal BF education is able to help women; at present, there is no good evidence from randomised controlled trials to suggest these efforts to educate pregnant women translate into more and longer BF. Women who receive standard care before birth tend to choose BF at about the same rate as women who have extra BF education. We are confident in the results of studies measuring women's uptake of BF at birth and BF at six months; education does not appear to impact these decisions. We have some doubts about the impact of education on exclusive BF at three and six months; education does not seem to help women, but future studies may change our understanding. Future studies are likely to change our understanding of the impact of BF education during pregnancy on BF at three months. Most of the studies in this review took place in higher income countries, so we are not confident that our conclusions are relevant in other settings.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

BF education versus standard/routine care						
Patient or population: pregnant women Setting: outpatient antenatal care at hospitals and clinics in Australia, Canada, Denmark, Hong Kong, Singapore, UK and USA Intervention: any antenatal BF education Comparison: standard/routine care						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Standard/ routine care	Risk with Summary of findings: One BF education				
Initiation of BF	Study population		average RR 1.01 (0.94 to 1.90)	3505 (8 RCTs)	⊕⊕⊕⊕ HIGH ¹	We have not downgraded any outcome for lack of blinding. No trial contributing data had adequate blinding of staff and participants
	750 per 1000	758 per 1000 (705 to 818)				
Proportion of women exclusively BF at 3 months	Study population		RR 1.06 (0.90 to 1.25)	822 (3 RCTs)	⊕⊕⊕○ MODERATE ²	
	376 per 1000	398 per 1000 (338 to 470)				
Proportion of women exclusively BF at 6 months	Study population		RR 1.07 (0.87 to 1.30)	2161 (4 RCTs)	⊕⊕⊕○ MODERATE ³	
	154 per 1000	165 per 1000 (134 to 201)				
Proportion of women any BF at 3 months	Study population		average RR 0.98 (0.82 to 1.18)	654 (2 RCTs)	⊕⊕○○ LOW ⁴⁵	
	609 per 1000	597 per 1000 (500 to 719)				

Proportion of women any BF at 6 months	Study population	average RR 1.05 (0.90 to 1.23)	1636 (4 RCTs)	⊕⊕⊕⊕ HIGH ⁶	
	505 per 1000 531 per 1000 (455 to 621)				
Breastfeeding complications	Duffy 1997 (n = 70) reported no group differences for mastitis, but less nipple pain and less nipple trauma for women who had a lactation consultant. ² Kronborg 2012 (n = 1162) reported no group differences as to whether women responded yes when asked about BF problems. ³		(2 studies)	Moderate	Both trials compared the intervention with standard care
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;					
GRADE Working Group grades of evidence High quality: We are very confident that the true effect lies close to that of the estimate of the effect Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect					

¹ Statistical heterogeneity $I^2 = 69\%$ (not downgraded)

² Downgraded for imprecision due to small sample size (-1).

³ Downgraded for imprecision due to wide confidence intervals crossing the line of no effect (-1).

⁴ Statistical heterogeneity $I^2 = 60\%$ (not downgraded)

⁵ Wide confidence intervals crossing the line of no effect and small sample size (-2)

⁶ Statistical heterogeneity $I^2 = 61\%$ (not downgraded)

BACKGROUND

Description of the condition

Breastfeeding (BF) is well recognised as the best food source for infants (Sankar 2015). Complementary foods offered before six months of age tend to displace breast milk and do not confer any health advantage over exclusive BF (Kramer 2012). BF has been advocated to improve child health, maternal health and mother-infant bonding (Ball 2001; Hanson 2002). BF has been associated with lower rates of gastrointestinal and respiratory diseases, otitis media and allergies, better visual acuity, and speech and cognitive development (Innis 2001; Quigley 2012; Renfrew 2012; Wold 2000). It is also cost effective (Renfrew 2012). Infants who are breastfed have a lower risk of developing insulin-dependent diabetes in childhood (Horta 2015), sudden infant death syndrome (Renfrew 2012) and childhood cancer (Amitay 2016). Recent research indicates that the type of infant feeding may contribute to children becoming overweight and obese in early and late childhood. BF has been shown to protect against child obesity and cardiovascular risk outcomes and is dose related - the longer the infant is breastfed, the lower the risk (Arenz 2004; Harder 2005; Owen 2005). A Cochrane Review by Kramer 2012 indicated that exclusive BF for six months has several advantages over exclusive BF for three to four months followed by mixed BF.

Delay in return of fertility has been associated with frequent and long periods of exclusive BF, as well as a lower risk of developing breast cancer (Chowdhury 2015). Women who had not breastfed their babies were four times more likely to have osteoporosis than women who had breastfed (Blaauw 1994). Better emotional health has also been attributed to women who breastfed. Virden 1988 found that, at one month postpartum, women who breastfed their infants had scores indicating less anxiety than women who had bottle fed their infants. The retrospective review of medical records of 800 pregnancies by Acheson 1995 revealed an association between lack of BF and physical and sexual abuse of the women or her children, or both. This was a small review, the results of which warrant further study. A recent published study found that women who breastfed for at least one year were less likely to develop Type 2 diabetes than women who did not breastfeed (Stuebe 2005). Some studies have shown a benefit of BF in enhancing couple and family relationships (Cohen 2002; Falceto 2004; Jordan 1993; Li 2004; Sullivan 2004).

In 1988, the World Health Organization (WHO) and UNICEF proposed the following standard terminology for the collection and description of data on BF behaviour; these were updated in 1991 (WHO 1991), and are now widely used (Dettwyler 1992). Breastfeeding means the infant receives breast milk but allows the infant to receive any food or liquid including non-human milk. Exclusive BF is defined as an infant being fed only breast milk, with the possible exception of vitamin D in certain populations and iron in infants of relatively low birthweight (Dewey 2001).

Predominant BF is when the infant receives breast milk as the predominant source of nourishment but allows the infant to receive liquids (water and water-based drinks, fruit juice, oral dehydration solutions) and drops or syrups (vitamins, minerals, medicines) but does not allow the infant to receive anything else (in particular, non-human milk and food-based fluids). Complimentary BF is the situation when the infant receives breast milk and solid or semi-solid foods and allows the infant to receive any food or liquid including non-human milk.

Despite the many advantages and extensive promotion of BF, Susin 1999 reported that the trend towards BF in many countries has been increasing slowly. However, according to the UNICEF report (UNICEF 2005), six million lives a year are being saved by exclusive BF and global BF initiation rates have risen by at least 15% since 1990. At the same time, women breastfeed for a shorter time than they intended or wished to (Adams 2001; Wagner 2002). The World Health Organization recommends that infants should be exclusively breastfed from birth to six months and then breastfed alongside age-appropriate, complementary feeding for two years and beyond (WHO 2001).

Description of the intervention

Antenatal BF education is defined as BF information being imparted during the pregnancy in a variety of forms. This could be on an individual or group basis, could include home visiting programmes, peer education programmes or clinic appointments specifically aimed at imparting BF knowledge and could involve prospective fathers or not. BF education is usually a formalised, defined, descriptive and goal-orientated programme with a specific purpose and target audience.

BF education differs from BF support. BF support is usually aimed at the individual person as the need arises and is defined as a person, a group or an organisation providing support in many ways. This could be psychological support (affirming and encouraging the mother), physical support (providing meals, caring for her other children, house cleaning and gardening), financial support or BF information services available to be tapped into when a BF question arises. BF support usually starts in the postnatal period, not antenatally.

Although we recognise the potential importance of interventions in the postnatal period on BF outcomes, the focus of this review is on antenatal BF education only, and we have not included trials examining interventions that also involve intrapartum or postpartum BF education. Other Cochrane Reviews examine BF education and support interventions in the intrapartum and postnatal periods (Britton 2007; Dyson 2005; Sikorski 2002).

How the intervention might work

Another Cochrane Systematic Review provides evidence that various forms of BF education are effective at increasing rates of BF initiation among women on low incomes in the USA and initiation will, therefore, not be the main focus in this review (Dyson 2005). The impact of antenatal BF education on the duration of BF, however, has not been widely reported. In Australia, more than 90% of mothers initiate BF; however, only 48% of mothers are BF at one month postpartum and only 23% maintain any form of BF at six months (Lund-Adams 1996). Similar BF duration rates have been reported in the USA (Raj 1998) and Britain (Griffiths 2005; Hoddinott 2000), as well as in low-income countries (UNICEF 1998). A variety of BF promotion methods including educational programmes have been studied to support the trend to increase BF duration. It is generally believed that, by improving the mothers' knowledge of BF antenatally, the rates and duration of BF would increase (McLeod 2002). Lack of antenatal information and education about BF has been one factor attributed by New Zealand mothers interviewed about discontinuing BF (McLeod 2002).

Why it is important to do this review

This is an update of a Cochrane Review first published in 2011, and previously updated in 2012. The earlier version of the review indicated that there were significant methodological limitations and the observed effect sizes were small, and there was no clear evidence to support any specific antenatal BF education. This current update will provide the most up-to-date evidence on the effectiveness of antenatal BF education.

OBJECTIVES

1. To assess the effectiveness of antenatal breastfeeding (BF) education for increasing BF initiation and duration.
2. To compare the effectiveness of various forms of education; for example, peer support, educational programme, didactic teaching session, workshop, booklets, etc, or a combination of these interventions for increasing BF initiation and duration.
3. To assess the effects of antenatal BF education on other maternal and infant outcomes, for example, BF complications, maternal satisfaction and neonatal sepsis.

METHODS

Criteria for considering studies for this review

Types of studies

All identified published, unpublished and ongoing randomised controlled trials (RCTs) comparing antenatal breastfeeding (BF) education programmes, with or without formal BF education. Randomised units could be clustered, for example, hospitals, communities or groups of pregnant women or individual women. We excluded quasi-RCTs. We did not include studies published only as abstracts.

Types of participants

Pregnant women or their partners, or both.

Types of interventions

Any type of antenatal education with BF components. Antenatal BF education is defined as BF information being imparted during pregnancy in a variety of forms. This could be on an individual or group basis, include home visiting programmes; peer education programmes or clinic appointments specifically aimed at imparting BF knowledge; brochures or booklets; electronic education programmes; or a combination of these, and could involve prospective fathers or not. Formal BF education is defined as BF education that was given formally in addition to any BF education that was given as part of standard antenatal care. We excluded RCTs examining interventions that included intrapartum or postpartum BF education in addition to antenatal BF education. We examined five comparisons.

1. One type of BF education versus standard/routine care
2. One type of BF education versus a different type of BF education
3. Multiple methods of BF education versus a single method of BF education
4. Different combinations of multiple methods of providing BF education
5. Multiple methods of BF education versus standard/routine care

Types of outcome measures

Primary outcomes

1. Duration of any BF
2. Duration of exclusive BF
3. Proportion of women with any BF at three and six months
4. Proportion of women exclusively BF at three and six months
5. Initiation of BF

Secondary outcomes

1. Maternal satisfaction
2. BF complications such as mastitis and breast abscess
3. Infant growth by weight and head circumference
4. Neonatal sepsis
5. Taking child to doctor
6. Hospital admission for child

Search methods for identification of studies

The following methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth.

Electronic searches

We searched Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (1 March 2016).

The Register is a database containing over 22,000 reports of controlled trials in the field of pregnancy and childbirth. For full search methods used to populate Pregnancy and Childbirth's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about the [Cochrane Pregnancy and Childbirth Group](#) in *The Cochrane Library* and select the '*Specialized Register*' section from the options on the left side of the screen.

Briefly, Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set which has been fully accounted for in the relevant review sections ([Included studies](#); [Excluded studies](#); [Studies awaiting classification](#); [Ongoing studies](#)).

In addition, we also searched CENTRAL (*The Cochrane Library*, 2016, Issue 3), MEDLINE (1966 to 1 March 2016) and Sco-

pus (January 1985 to 1 March 2016). We contacted experts and searched reference lists of retrieved articles using the search strategies detailed in [Appendix 1](#).

Searching other resources

We contacted investigators (identified from the retrieved articles) and other content experts known to us for unpublished studies. Furthermore, we looked for relevant studies in the references of the retrieved articles.

We did not apply any language or date restrictions.

Data collection and analysis

For methods used in the previous version of this review, see [Lumbiganon 2012](#).

For this update, we used the following methods for assessing the 42 reports that we identified as a result of the updated search.

The following methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted the third review author.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted the third review author. Data were entered into Review Manager (RevMan) software ([RevMan 2014](#)) and checked for accuracy.

When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011a](#)). We resolved any disagreement by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding was unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at

each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we planned to re-include missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we had about other possible sources of bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011a). With reference to (1) to (6) above, we planned to assess the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. In future updates, we will explore the impact of the level of bias through undertaking sensitivity analyses - see [Sensitivity analysis](#).

Assessment of the quality of the evidence using the GRADE approach

For this update the quality of the evidence was assessed using the GRADE approach as outlined in the [GRADE handbook](#), in order to assess the quality of the body of evidence relating to the

following outcomes for comparison 6. Any BF education versus standard care:

1. Initiation of BF
2. Proportion of women exclusively BF at six months
3. Proportion of women exclusively BF at three months
4. Proportion of women with any BF at six months
5. Proportion of women with any BF at three months
6. BF complications such as mastitis and breast abscess

GRADEpro Guideline Development Tool was used to import data from RevMan (RevMan 2014) in order to create a 'Summary of findings' table. A summary of the intervention effect and a measure of quality for each of the above outcomes was produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

For dichotomous data, we presented results as summary risk ratio (RR) with 95% confidence intervals (CI), with the exception of cluster-randomised trials that reported adjusted odds ratios (OR) (see note below). For continuous data we used the mean difference (MD) if outcomes were measured in the same way between trials. In future updates, if appropriate, we will use the standardised mean difference to combine trials that measured the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

We included studies where individual women were randomised and cluster-randomised studies where, for example, clinics were the unit of randomisation. Five included studies were cluster-randomised trials (Flax 2014; Kools 2005; Lavender 2005; MacArthur 2009; Mattar 2007); all of these studies report results for review outcomes with adjustments made for clustering effects. For trials where cluster-adjusted data were reported as odds ratios (Flax 2014; Kools 2005; Lavender 2005; MacArthur 2009; Mattar 2007) we have analysed the data using the generic inverse variance method in RevMan 2014; we presented these results as odds ratios, because we were unable to derive a cluster-adjusted risk ratio from the published, cluster-adjusted odds ratio. We acknowledge that the use of odds ratios prevents the pooling of these cluster trials in our main analyses (comparison 6).

Where there was no adjustment for cluster design effect in the published report, or where raw data were available, we adjusted

the data ourselves and have presented risk ratios, because we feel this statistic is more appropriate for BF outcomes. (For example, Lavender 2005 provides an intra-cluster correlation co-efficient (ICC) of 0.01, as well as mean cluster size and design effects for each BF outcome; we used these to adjust the sample size for outcome data in Analysis 1.5). If we adjusted data ourselves, we combined the adjusted data in analyses and report pooled risk ratios. We consider it reasonable to combine the results from both individual and cluster-randomised trials if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

In future updates, if we identify any more cluster-randomised trials we will include them in the analyses along with individually-randomised trials. If adjustment for the cluster design effect has not already been made by the trial authors, we will adjust their sample sizes using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions*; Section 16.3.4 or 16.3.6 (Higgins 2011b) using an estimate of the ICC derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC.

We will also acknowledge heterogeneity in the randomisation unit, and, if there are sufficient numbers of trials, we will perform a subgroup analysis to investigate the effects of the randomisation unit.

Cross-over trials

Cross-over trials were not eligible for this review.

Other unit of analysis issues

Multiple pregnancies

In the studies that contributed data to this review, four excluded multiple pregnancies from their trial (Kellams 2016; Kronborg 2012; Mattar 2007; Wong 2014). Of the remaining studies, 12 did not mention multiple pregnancies (Duffy 1997; Flax 2014; Forster 2004; Kistin 1990; Kluka 2004; Kools 2005; Lavender 2005; MacArthur 2009; Olenick 2010; Schlickau 2005a; Schlickau 2005b; Wolfberg 2004). Serwint 1996 was the only study that reported a twin pregnancy and only included data from twin A. We have not made adjustments to any analyses to account for correlated outcomes due to multiple pregnancy.

Multiple-armed studies

Four studies contributing data to our review included multiple treatment arms (Forster 2004; Kistin 1990; Mattar 2007; Schlickau 2005a). Ryser 2004 also included multiple treatment arms but did not contribute any data to this review.

We treated trials with three arms as follows.

1. We included two intervention arms comparing one form of BF education versus another form (group antenatal BF class and individual antenatal counselling) in Comparison 2 (Kistin 1990). In this study, the third comparison arm was a control group which was not randomised and therefore not included in this review.

2. We included only the intervention arms comparing an information booklet, educational video and session with a lactation consultant versus the same information booklet and video without the lactation consultant session in Comparison 4 (Mattar 2007), the third comparison was a control group and was included in Comparison 5.

3. For comparisons 1 to 5, we included more than one intervention arm compared with control, so the study ID will appear in the forest plot twice (a footnote identifies the arms). We did not split the control groups for these analyses because the trials were not pooled.

4. We kept intervention arms separate and split the control group to avoid double counting for pooled data in Comparison 6 (Forster 2004).

5. Schlickau 2005a presented continuous data, and so we compared single intervention arms with control.

Dealing with missing data

For included studies, we noted levels of attrition. In future updates, if more eligible studies are included, we will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, that is, we attempted to include all participants randomised to each group in the analyses. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the τ^2 , I^2 (Higgins 2003) and χ^2 statistics. We regarded heterogeneity as substantial if I^2 was greater than 30% and either τ^2 was greater than zero, or there was a low P value (less than 0.10) in the χ^2 test for heterogeneity. If we identified substantial heterogeneity (above 30%), we planned to explore it by pre-specified subgroup analysis (Deeks 2011).

Assessment of reporting biases

In future updates, if there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager (RevMan) software (RevMan 2014). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: that is, where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar.

If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary if an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we planned not to combine trials. If we used random-effects analyses, the results were presented as the average treatment effect with 95% confidence intervals, and the estimates of τ^2 and I^2 .

Subgroup analysis and investigation of heterogeneity

Where we identified substantial heterogeneity, we planned to investigate it using subgroup analyses and sensitivity analyses. We used a random-effects model if the overall summary was meaningful.

We planned to carry out the following subgroup analyses.

1. Type of intervention
2. Study setting
3. Maternal education
4. Maternal occupation

We planned to restrict subgroup analysis to primary outcomes with sufficient numbers of trials in the relevant subgroups and to assess subgroup differences by interaction tests available within RevMan (RevMan 2014). We planned to report the results of subgroup analyses quoting the χ^2 statistic and P value, and the interaction test I^2 value.

There were insufficient trials in relevant subgroups to analyse subgroups according to types of interventions or setting. There were insufficient trials reporting outcome data according to maternal education or maternal occupation to conduct these subgroup analyses.

Sensitivity analysis

We planned to explore the effect of trial quality assessed by concealment of allocation, high attrition rates, or both, with poor-quality studies being excluded from the analyses in order to assess whether this made any difference to the overall result. There were no studies at high risk of bias for allocation concealment, so we did not conduct this analysis. When we removed one trial at high risk of bias for attrition (Wolfberg 2004) results did not change for Analysis 6.1 (analysis not shown).

RESULTS

Description of studies

Results of the search

In the first published version of this review (Lumbiganon 2011) the search of the Pregnancy and Childbirth Group's Trials Register yielded 57 potential studies. Our additional search yielded one potential study. We explored the contents, and grouped together trial reports for the same study; from this we identified 17 studies (involving 7131 women) that met the inclusion criteria. We excluded 39 studies.

In the subsequent version (Lumbiganon 2012) of this review we searched the Pregnancy and Childbirth Group's Trials Register on 2 December 2011 and in addition, we searched CENTRAL (*The Cochrane Library*, 2011, Issue 11), MEDLINE (1966 to 30 November 2011) and Scopus (January 1985 to 30 November 2011) using the search strategies detailed in Appendix 1. We identified five additional potential studies, two studies (Kronborg 2012; Olenick 2010) were included, and three excluded (Kupratkul 2010; NCT01383070; Wockel 2009). We therefore included 19 studies involving 8506 women and excluded 42 studies in that update.

For this update (2016) we searched Pregnancy and Childbirth's Trials Register (1 March 2016), CENTRAL (*The Cochrane Library*, 2016, Issue 3), MEDLINE (1966 to 1 March 2016) and Scopus (January 1985 to 1 March 2016). We identified 42 citations of which there were nine potential included studies. We have included five more studies (Flax 2014; Kellams 2016; Pate 2009; Raeisi 2014; Wong 2014) at this update.

Two studies are awaiting translation and classification (Bahri 2013; Bastani 2009) and one study is ongoing (Maycock 2015). For the 2016 update we have included a total of 24 studies and excluded at total of 66 studies.

Included studies

We included 24 studies. We have provided full details of included studies in the [Characteristics of included studies](#) tables. Of these, 20 studies involving 9789 women contributed data to the analyses for primary and secondary outcomes; four included studies (Kaplowitz 1983; Noel-Weiss 2006; Pate 2009; Ryser 2004) met our inclusion criteria but did not report data on any of our prespecified outcomes. Kaplowitz 1983 described women's attitudes towards breastfeeding (BF) before and after the intervention and we have not included results from this study in the review. Ryser 2004 and Noel-Weiss 2006 report on BF at time points which we had not prespecified, and we have included a brief description of results from these studies following results for our primary and secondary outcomes. Pate 2009 reported self-efficacy outcomes which were not prespecified outcomes in this review.

Study design

We included 19 randomised controlled trials and five cluster randomised trials (Flax 2014; Kools 2005; Lavender 2005; MacArthur 2009; Mattar 2007). Five studies included multiple treatment arms (Forster 2004; Kistin 1990; Mattar 2007; Ryser 2004; Schlickau 2005a).

Sample sizes

We included 24 studies with 10,056 women in the review, and 20 studies involving 9789 women contributed data to the analyses. The sample size of studies that contributed data to the review ranged from 30 (Schlickau 2005a) to 2511 (MacArthur 2009) with an average of 419 women. Six of these studies had fewer than 100 women taking part (Duffy 1997; Finch 2002; Kistin 1990; Schlickau 2005a; Schlickau 2005b; Wolfberg 2004).

Setting

Eleven studies were conducted in the USA (Finch 2002; Kaplowitz 1983; Kellams 2016; Kistin 1990; Olenick 2010; Pate 2009; Ryser 2004; Schlickau 2005a; Schlickau 2005b; Serwint 1996; Wolfberg 2004), three in Australia (Duffy 1997; Forster 2004; Rossiter 1994), two in the United Kingdom (Lavender 2005; MacArthur 2009), two in Canada (Kluka 2004; Noel-Weiss 2006), one in Iran (Raeisi 2014), one in Nigeria (Flax 2014), one in the Netherlands (Kools 2005), one in Denmark (Kronborg 2012), one in Singapore (Mattar 2007), and one in Hong Kong (Wong 2014). Overwhelmingly the evidence in this review is relevant to higher income countries and settings.

Participants

All 24 studies recruited women in the antenatal period who were accessing antenatal care services with the exception of Flax 2014 who recruited women attending monthly microcredit meetings. Nine studies only recruited primigravida women (Forster 2004; Kluka 2004; Kronborg 2012; Noel-Weiss 2006; Pate 2009; Schlickau 2005a; Schlickau 2005b; Serwint 1996; Wong 2014). Kaplowitz 1983 included primigravida women, women who had bottle-fed previous children or who had previously had an unsuccessful BF experience.

The studies recruited at a range of gestations for example Rossiter 1994 recruited pregnant women who were at least 12 weeks' gestation, Forster 2004 and Kaplowitz 1983 at 16 to 24 weeks' gestation and Mattar 2007 at gestations above 36 weeks.

Kellams 2016; Pate 2009 and Ryser 2004 only recruited women on a low income, though only Kellams 2016 contributed data to the review.

None of the studies specified ethnicity except for Kistin 1990, who recruited only black women born in the USA, and Rossiter 1994, who only recruited Vietnamese or other women who were born and reared in Vietnam.

Four studies only recruited women with singleton pregnancies (Kronborg 2012; Mattar 2007; Noel-Weiss 2006; Wong 2014). Wolfberg 2004 and Raeisi 2014 recruited pregnant women's partners to antenatal BF education.

Interventions and comparisons

Interventions included BF education session, printed information, video, peer counselling and lactation consultation (LC), weekly cell phone BF text and voice messages to cell phone, web-based education, and support related to BF practices.

There were a total of 20 comparisons from the included studies which are described below (some studies with more than two experimental arms are included in more than one comparison).

Sixteen studies compared a single method of BF education with standard care (Duffy 1997; Forster 2004; Kaplowitz 1983; Kellams 2016; Kluka 2004; Kronborg 2012; Lavender 2005; MacArthur 2009; Noel-Weiss 2006; Olenick 2010; Raeisi 2014; Schlickau 2005a; Schlickau 2005b; Serwint 1996; Wolfberg 2004; Wong 2014). Two of these studies (Kaplowitz 1983; Noel-Weiss 2006) compared BF education session versus standard care but did not provide any information about BF practices. Seven studies (Forster 2004; Kronborg 2012; Lavender 2005; Olenick 2010; Raeisi 2014; Schlickau 2005a; Wong 2014) compared BF education session versus standard care. Two studies (Duffy 1997; Serwint 1996) compared LC versus standard care. Two studies (Kluka 2004; Schlickau 2005b) compared BF workshop versus standard care. One study (Kellams 2016) compared BF video versus standard care. Two studies (MacArthur 2009; Raeisi 2014) compared BF peer support versus standard care. Raeisi 2014 and Wolfberg 2004 both aimed interventions at partners of pregnant women.

There were two studies (Forster 2004; Kistin 1990) comparing one form of BF education versus other form of BF education. One study (Kistin 1990) compared group education versus individual education. One study (Forster 2004) compared BF practical skills versus BF attitude education.

Three studies (Finch 2002; Rossiter 1994; Schlickau 2005a) examined programmes involving multiple methods of providing education compared to those using a single method. Finch 2002 compared LC plus incentive plus handout with BF education session. Rossiter 1994 examined the effect of a video and BF education session versus a BF pamphlet. One study (Schlickau 2005a) compared BF education session and baby quarantine versus BF education session.

Two studies (Kools 2005; Mattar 2007) compared different combinations of multiple interventions. One study (Mattar 2007) compared a BF booklet plus a video and LC versus a BF booklet and video only. Another study (Kools 2005) compared LC and a BF booklet with BF booklet and phone number for BF questions. There were four studies (Flax 2014; Mattar 2007; Ryser 2004; Schlickau 2005a) that compared programmes involving multiple methods of providing education versus standard care. Flax 2014

compared weekly cell phone BF text and voice messages to cell phone and monthly face-to-face BF information versus standard care. Mattar 2007 compared a BF booklet, video and LC versus no formal BF education. Ryser 2004 compared a counselling session plus viewing a video plus the provision of written materials addressing common BF barriers perceived by low-income women versus no formal BF education. This study did not provide any information on our proposed outcomes and has not been included in the analyses. Schlickau 2005a compared BF education session plus baby quarantine concept versus standard care.

In studies where BF education was compared with standard care, there was considerable variation in what was offered as part of usual care in terms of BF education. In many studies standard care was not described at all or the description was vague (e.g. provision of a leaflet or midwife advice). We have set out information about care for control groups in the [Characteristics of included studies](#), and it is important that this is taken into account in the interpretation of results. Intrapartum and postpartum care could also have an impact on BF duration; these aspects of care also varied across included studies.

Comparisons in the studies were mostly reported as 'routine' or 'standard' antenatal care. In 13 studies standard/routine care included some form of BF education or support (Finch 2002; Forster 2004; Kluka 2004; Kools 2005; Lavender 2005; MacArthur 2009; Mattar 2007; Pate 2009; Rossiter 1994; Schlickau 2005a; Schlickau 2005b; Serwint 1996; Wong 2014). Two studies did not include any BF information (Flax 2014; Wolfberg 2004), and it was not clear in the remaining nine studies whether the control group participants received any BF education or support as part of standard care (Duffy 1997; Kaplowitz 1983; Kellams 2016; Kistin 1990; Kronborg 2012; Noel-Weiss 2006; Olenick 2010; Raeisi 2014; Ryser 2004).

Excluded studies

We excluded 66 studies. Reasons for exclusion included: the intervention was not confined to the antenatal period only or was not an educational intervention, or the paper did not report on a randomised controlled study. For further details, see the [Characteristics of excluded studies](#) tables.

We have not considered educational and support interventions to promote BF in the intrapartum and postnatal periods in this review; related Cochrane Reviews (Britton 2007; Dyson 2005) examine these topics.

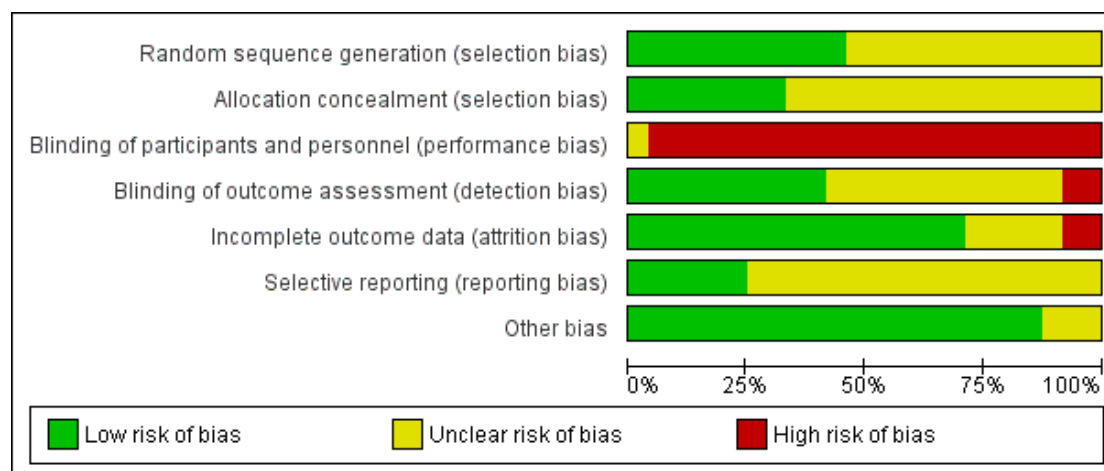
Risk of bias in included studies

We have provided details of risk of bias in each study in the [Characteristics of included studies](#) tables and the methodological quality summary (Figure 1) and methodological quality graph (Figure 2).

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Duffy 1997	?	?	+	+	?	?	+
Finch 2002	?	?	?	?	+	?	+
Flax 2014	?	?	+	+	+	+	+
Forster 2004	+	+	+	?	+	?	+
Kaplowitz 1983	?	?	+	?	?	?	?
Kellams 2016	+	+	+	+	+	+	+
Kistin 1990	+	?	+	?	?	?	+
Kluka 2004	?	+	+	+	+	?	+
Kools 2005	+	?	+	+	+	?	+
Kronborg 2012	+	?	+	+	+	+	+
Lavender 2005	?	+	+	+	+	?	+
MacArthur 2009	+	?	+	+	+	?	+
Mattar 2007	+	+	+	+	+	?	+
Noel-Weiss 2006	?	+	+	+	+	?	+
Olenick 2010	?	?	+	+	+	?	+
Pate 2009	+	?	+	?	+	+	?
Raeisi 2014	+	?	+	?	+	+	+
Rossiter 1994	?	?	+	?	?	?	+
Ryser 2004	?	?	+	?	+	?	+
Schlickau 2005a	?	?	+	?	?	?	?
Schlickau 2005b	?	+	+	?	+	?	+
Serwint 1996	+	?	+	?	+	?	+
Wolfberg 2004	?	?	+	?	+	?	+
Wong 2014	+	+	+	+	+	+	+

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies



Allocation

Eleven out of 24 included studies (Forster 2004; Kellams 2016; Kistin 1990; Kools 2005; Kronborg 2012; MacArthur 2009; Mattar 2007; Pate 2009; Raeisi 2014; Serwint 1996; Wong 2014) had adequate sequence generation for randomisation.

Eight out of 24 included studies (Forster 2004; Kellams 2016; Kluka 2004; Lavender 2005; Mattar 2007; Noel-Weiss 2006; Schlickau 2005b; Wong 2014) had adequate allocation concealment.

Blinding

Only 10 included studies (Duffy 1997; Flax 2014; Kellams 2016; Kluka 2004; Kronborg 2012; Lavender 2005; MacArthur 2009; Mattar 2007; Noel-Weiss 2006; Wong 2014) had implemented blinding; however, this blinding was only for the outcome assessors. This is perhaps mainly due to the nature of the interventions in that it was not possible to blind both women and educators. All studies were judged at high risk of performance bias except for Finch 2002 where blinding of participants and personnel was unclear.

Incomplete outcome data

Seventeen out of 24 included studies (Flax 2014; Forster 2004; Kellams 2016; Kluka 2004; Kools 2005; Kronborg 2012;

Lavender 2005; MacArthur 2009; Mattar 2007; Noel-Weiss 2006; Olenick 2010; Pate 2009; Raeisi 2014; Ryser 2004; Schlickau 2005b; Serwint 1996; Wong 2014) had low risk of attrition bias. Two studies (Finch 2002; Wolfberg 2004) had high risk of bias. Five studies (Duffy 1997; Kaplowitz 1983; Kistin 1990; Rossiter 1994; Schlickau 2005a) had unclear risk of bias.

Selective reporting

Since we did not have access to the protocols of most of the included studies, we assessed their risk of bias for selective reporting as unclear. In the current update, we assessed selective reporting as low risk of bias since all expected outcomes reported in the methods were reported in the results (Flax 2014; Kellams 2016; Pate 2009; Raeisi 2014; Wong 2014). We have also re-assessed one trial (Kronborg 2012) for this update and have changed risk of bias from unclear to low risk for selective reporting.

Other potential sources of bias

Three out of 24 included studies (Kaplowitz 1983; Pate 2009; Schlickau 2005a) had unclear risk of other potential sources of biases. All other studies had low risk of other sources of bias.

Effects of interventions

See: [Summary of findings for the main comparison Antenatal breastfeeding \(BF\) education versus standard care](#)

This review includes 24 studies with 10,056 women. However, for our primary and secondary outcomes only 20 studies with 9789 women contributed data for analyses and for most comparisons, only single studies contributed outcome data. For the first five comparisons in this review we display the included trials according to type of intervention without pooling data. However, for the 'Summary of findings' table we pooled data in order to provide evidence for a summary effect for the main comparison of BF education versus standard care. Some studies had more than two treatment arms and are included in more than one comparison ([Forster 2004](#); [Kistin 1990](#); [Mattar 2007](#); [Schlickau 2005a](#)) and some studies were cluster-randomised trials ([Flax 2014](#); [Kools 2005](#); [Lavender 2005](#); [MacArthur 2009](#); [Mattar 2007](#); [Schlickau 2005a](#)), and provided cluster-adjusted odds ratios and have been analysed using the generic inverse variance method.

We have presented effects of interventions for each comparison as follows.

I. One type of BF education versus standard/routine care

For this comparison we have presented evidence according to the type of intervention. We have not pooled the totals for this comparison.

We have reported results from cluster trials that presented cluster-adjusted odds ratios separately ([Lavender 2005](#); [MacArthur 2009](#)).

Primary outcomes

Duration of any BF

One study ([Olenick 2010](#)) involving 165 women reported the comparison of BF education session with standard care. The mean difference (MD) in duration of any BF in the two groups was very similar in both groups (MD 0.0 weeks, 95% CI -2.78 to 2.78 weeks; [Analysis 1.1](#)). Another study ([Schlickau 2005a](#)) involving 16 women reported the comparison of BF education session with standard care. The intervention group had a slightly longer mean duration of BF compared with the standard care group but the CI was wide and crossed the line of no effect (MD 6.20 months, 95% CI -10.84 to 23.24 months; [Analysis 1.1](#)).

Proportion of women any BF at three and six months

Any BF at three months [Analysis 1.2](#): [Kluka 2004](#) compared a BF education workshop with standard care. This study reported data for 185 women and no increases were found in BF at three months (RR 1.07, 95% CI 0.92 to 1.24; women = 185). [Wong 2014](#) found no group differences with a BF education session (RR 0.90, 95% CI 0.75 to 1.07; women = 469).

Any BF at six months [Analysis 1.3](#): In [Kluka 2004](#) there was very little difference in proportion of women exclusively BF at six months between the BF education group and the standard care group (RR 1.15, 95% CI 0.87 to 1.51; women = 178).

[Forster 2004](#) compared practical skills education with attitude education and standard care; there were no group differences in the intervention arms (skills: RR 1.01, 95% CI 0.87 to 1.17; women = 596; attitudes: RR 0.92, 95% CI 0.79 to 1.07; women = 592). [Wong 2014](#) and [Raeisi 2014](#) compared BF education session with standard care ([Raeisi 2014](#) targeted the intervention at partners of pregnant women) and found no evidence of group differences (RR 1.01, 95% CI 0.86 to 1.19; women = 569; studies = 2).

Proportion of women exclusively BF at three and six months

Exclusive BF at three months [Analysis 1.4](#): [Kluka 2004](#) compared a BF education workshop with standard care. This study reported data for 185 women and no differences were found in exclusive BF at three months (RR 1.08, 95% CI 0.84 to 1.38; women = 185). [Olenick 2010](#) and [Wong 2014](#) both tested BF education sessions against standard care with no evidence of group differences (RR 1.05, 95% CI 0.85 to 1.30; women = 637; studies = 2).

Exclusive BF at six months [Analysis 1.5](#): In [Kluka 2004](#) there were 178 women remaining in the sample at six months and proportion of women exclusively BF in each group was very similar (RR 1.13, 95% CI 0.70 to 1.80; women = 178). [Forster 2004](#) tested both skills education and attitudes education with no evidence for an impact on exclusive BF at this time point (skills: RR 1.19, 95% CI 0.69 to 2.05; women = 596; attitudes: RR 1.16, 95% CI 0.67 to 2.01; women = 592). [Wong 2014](#) and [Lavender 2005](#) did not detect group differences after an education session versus standard care (RR 1.02, 95% CI 0.80 to 1.31; women = 1094).

Initiation of BF

Single studies of different interventions were unable to show that education improved initiation of BF, apart from one small trial at high risk of attrition bias ([Wolfberg 2004](#)). Many trial results favoured the intervention but had wide confidence intervals crossing the line of no effect.

One study ([Schlickau 2005b](#)) involving 80 women compared a BF education workshop with standard care. There were no differences in initiation of BF between the two groups (RR 1.19, 95% CI 0.97 to 1.45; women = 80; [Analysis 1.6](#)). A study by [Wolfberg 2004](#) involving partners of 59 women comparing peer counselling versus standard care showed an increase in the initiation of BF in the intervention group (RR 1.82, 95% CI 1.13 to 2.93; women = 59; [Analysis 1.6](#)). Another study ([Forster 2004](#)) compared BF practical skills education versus standard care and BF attitudes education versus standard care. Again, the number of women initiating BF was similar in both groups (skills: RR 1.01, 95% CI 0.98 to 1.04; women = 616; attitude: RR 0.99, 95% CI

0.95 to 1.02; women = 618; [Analysis 1.6](#)). Two further studies ([Kronborg 2012](#); [Olenick 2010](#)) compared BF education sessions with standard care and showed no differences in initiation rate of BF between the two groups (pooled subtotal RR 1.03, 95% CI 0.98 to 1.09; women = 1327; [Analysis 1.6](#)). One study ([Kellams 2016](#)) with 346 women compared BF education video with standard care and, again, showed no difference in numbers of women initiating BF (RR 0.99, 95% CI 0.80 to 1.23; [Analysis 1.6](#)). Another study ([Serwint 1996](#)) with 144 women compared LC with standard care also showed no difference between the groups in initiation of BF (RR 1.33, 95% CI 0.86 to 2.07; [Analysis 1.6](#)). Two cluster-randomised trials reported adjusted odds ratios for this outcome, and reported peer counselling ([MacArthur 2009](#)) and group LC session ([Lavender 2005](#)) versus standard care. Both studies found women who received the intervention were slightly more likely to initiate BF, however both studies had wide confidence intervals, which crossed the line of no effect ([MacArthur 2009](#) OR 1.11, 95% CI 0.86 to 1.43; women = 2398; [Lavender 2005](#) OR 1.20, 95% CI 0.80 to 1.80; women = 1249; [Analysis 1.7](#)).

Duration of exclusive BF

This was not reported in any trials in this comparison.

Secondary outcomes

BF complications (mastitis, nipple trauma and pain)

[Duffy 1997](#) compared LC versus standard care. There was no difference in numbers of women with mastitis between the groups (RR 0.20, 95% CI 0.01 to 4.02; women = 70; [Analysis 1.8](#)). However, a reduction in nipple pain as measured by visual analogue scale (VAS) scores was recorded (MD -19.80, 95% CI -23.23 to -16.37; women = 70; [Analysis 1.9](#)). The VAS ranged from 0 to 10 with a '0' representing 'no pain' and an increase to a maximum of 10 representing 'pain as bad as it could possibly be'. In the same study, less nipple trauma measured by nipple trauma index (NTI) scores was reported for the LC group (MD 38.65, 95% CI 32.95 to 44.35; women = 70; [Analysis 1.10](#)). The possible range of NTI was 0 to 34 with a higher NTI score indicating less trauma. One study ([Kronborg 2012](#)) with data for 1162 women compared group training programme with standard care and showed no differences in numbers of women reporting BF problems (RR 1.00, 95% CI 0.70 to 1.43; women = 1162; [Analysis 1.11](#)).

Secondary outcomes **maternal satisfaction, neonatal sepsis, taking child to doctor, and hospital admission for child** were not reported by any trials in this comparison. [Raeisi 2014](#) reported no difference in infant weight gain between the intervention and control groups but the data was not in a format that could be included in an analysis.

Non-prespecified outcomes

Two studies reported BF practices at time points not pre-specified for this review. One study ([Noel-Weiss 2006](#)) compared a BF education workshop with standard care. It involved 92 women and no significant increases were reported for BF at eight weeks (RR 0.91, 95% CI 0.75 to 1.11) and exclusive BF at eight weeks (RR 0.82, 95% CI 0.60 to 1.12) (data not shown in data and analyses tables). Another study ([Ryser 2004](#)) compared a BF education programme with standard care. It involved 54 women and outcomes were reported at seven days; at this time point significant increases were reported in BF (RR 1.21, 95% CI 1.03 to 1.42) (data not shown in data and analyses tables).

2. One type of BF education versus a different type of BF education

Primary outcomes

Proportion of women any BF at three and six months

Any BF at three months: one study ([Kistin 1990](#)) involving 74 women compared group discussion versus individual discussion and reported the women who received group discussion were very slightly more likely to be BF at three months but the CIs for this data were very wide and crossed the line of no effect (RR 2.84, 95% CI 0.61 to 13.18; [Analysis 2.1](#)).

Any BF at six months: [Forster 2004](#) compared BF practical skills education versus BF attitudes education. This study reported data for 590 women and found similar proportions of women were BF at six months in each group (RR 1.09, 95% CI 0.94 to 1.28; [Analysis 2.2](#)).

Proportion of women exclusively BF at three and six months

No trial included in this comparison reported exclusive BF at three months.

Exclusive BF at six months: [Forster 2004](#) also reported no differences between the women receiving practical skills education versus BF attitudes education who were exclusively BF at six months (RR 1.03, 95% CI 0.61 to 1.73; women = 590; [Analysis 2.3](#)).

Initiation of BF

One study ([Forster 2004](#)) involving 614 women compared BF practical skills education versus BF attitudes education. There was no difference between the numbers of women in each group who initiated BF (RR 1.02, 95% CI 0.99 to 1.06; women = 614; [Analysis 2.4](#)).

Duration of any BF, duration of exclusive BF, and proportion of women exclusively BF at three months were not reported in any trials in this comparison.

Secondary outcomes

No secondary outcomes were reported in this comparison.

3. Multiple methods of BF education versus a single method of BF education

There were limited trials available for this comparison, with most outcomes not reported.

Primary outcomes

Duration of any BF

One study (Schlickau 2005a) involving 18 women compared BF education session plus commitment to exclusive BF versus BF education session. Although women receiving multiple interventions appeared to breastfeed for slightly more days than those receiving a single intervention, the CI was wide and crossed the line of no effect (MD 8.00 days, 95% CI -6.84 to 22.84 days; Analysis 3.1).

Proportion of women any BF at three and six months

Any BF at six months: the study by Rossiter 1994, involving 175 women compared video plus BF education session with the provision of pamphlets. There was no evidence of a difference in BF at six months between the two groups (RR 1.59, 95% CI 0.86 to 2.94; Analysis 3.2).

Duration of exclusive BF, proportion of women any BF at three months, proportion of women exclusively BF at three and six months, and initiation of BF were not reported in any trials in this comparison.

Secondary outcomes

No secondary outcomes were reported in this comparison.

4. Different combinations of multiple methods of providing BF education

All trials contributing data for this comparison at this update were cluster-randomised trials. We have presented the cluster-adjusted odds ratios as reported (Kools 2005; Mattar 2007).

Primary outcomes

Proportion of women any BF at three and six months

Three months: Kools 2005, with 698 women, compared LC plus BF booklet plus 24-hour free LC versus BF booklet plus phone number for BF questions and problems; the trial reported similar

rates of BF in both groups (adjusted OR 0.82, 95% CI 0.58 to 1.16; Analysis 4.1).

Proportion of women exclusively BF at three and six months

Three months: Kools 2005 also reported no evidence of a difference in exclusive BF at three months (adjusted OR 0.79, 95% CI 0.57 to 1.09; women = 698; Analysis 4.2). Another study (Mattar 2007) compared BF booklet plus video plus LC versus BF booklet plus video. Again, the study reported no evidence of a difference in exclusive BF at three months (OR 1.40, 95% CI 0.70 to 2.80; women = 150; Analysis 4.2).

Six months: Mattar 2007 reported a marginal increase in exclusive BF in the group receiving a booklet plus video plus LC compared with the group who received a booklet plus video only (OR 2.50, 95% CI 1.00 to 6.25; women = 169; Analysis 4.3).

Duration of any BF, duration of exclusive BF, proportion of women any BF at six months, and initiation of BF were not reported in any trials in this comparison.

Secondary outcomes

No secondary outcomes were reported in this comparison.

5. Multiple methods of BF education versus standard/routine care

Two trials (Flax 2014; Mattar 2007) included in this comparison at this update were cluster-randomised trials. For categorical variables we have presented the cluster-adjusted odds ratios as reported in trial publications.

Primary outcomes

Duration of any BF

One study (Schlickau 2005a) involving 16 women compared BF education session plus commitment to BF versus standard care. Women in the BF education session plus commitment group breastfed for more days than those who only received standard care, however, the data for this outcome had a wide CI, which crossed the line of no effect (MD 14.20 days, 95% CI -2.97 to 31.37 days; Analysis 5.1).

One study (Finch 2002) involving 48 women compared LC plus incentive versus standard care; there were no significant differences in duration of BF between intervention and control group (median 12 versus six weeks, data not shown in the analysis).

Proportion of women exclusively BF at three and six months

Exclusive BF at three months [Analysis 5.2](#): one three-arm study ([Mattar 2007](#)) involving 234 women. We have reported each intervention arm compared with control, so [Mattar 2007](#) appears twice in the forest plot. The intervention of BF booklet plus video plus LC versus standard care improved rates of exclusive BF (OR 2.60, 95% CI 1.25 to 5.40; women = 159). The intervention arm without a LC but with the BF booklet and video did not have the same effect on exclusive BF at three months (OR 1.80, 95% CI 0.80 to 4.05; women = 159). [Flax 2014](#), involving 461 women, compared monthly BF sessions plus weekly cell phone message versus standard care and reported women in the intervention group were more likely than those in the standard care group to be exclusively BF at three months (OR 1.80, 95% CI 1.10 to 2.95; women = 390).

Exclusive BF at six months [Analysis 5.3](#): at six months similar patterns of increase in exclusive BF of the three comparisons were presented. [Mattar 2007](#) had marginal results for the intervention arm including an LC, but not otherwise (with LC OR 2.40, 95% CI 1.00 to 5.76; women = 175; without LC OR 0.90, 95% CI 0.30 to 2.70; women = 184). [Flax 2014](#) found no group differences (OR 2.40, 95% CI 1.40 to 4.11; women = 390).

Initiation of BF

One study ([Flax 2014](#)), involving 461 women, compared monthly BF sessions plus weekly cell phone message versus standard care and reported that those in the intervention group were more likely to initiate of BF (OR 2.61, 95% CI 1.61 to 4.24; women = 380; [Analysis 5.4](#)).

Duration of exclusive BF and proportion of women any BF at three and six months were not reported in any trials in this comparison.

Secondary outcomes

No secondary outcomes were reported in this comparison.

6. Summary of findings: one type of BF education versus standard/routine care

There was no evidence that antenatal education of any sort could improve the initiation or duration of BF over the standard care offered to pregnant women. It is important to bear in mind that of the 20 studies contributing data to this review, 13 had BF education or support as part of the standard care comparator. Cluster trials presenting adjusted odds ratios were not included in this comparison. We expected substantial heterogeneity due to the different interventions and settings of trials. We used a random-effects model for all analyses with high heterogeneity ([Analysis 6.1](#); [Analysis 6.4](#); and [Analysis 6.5](#)). For the summary of findings we used pooled effects of any BF education versus standard care.

No differences were observed between groups for any of the following outcomes.

1. Initiation of BF (average RR 1.01, 95% CI 0.94 to 1.09; women = 3505; studies = 8; $I^2 = 69\%$; [Analysis 6.1](#); high-quality evidence)

2. Proportion of women exclusively BF at three months (RR 1.06, 95% CI 0.90 to 1.25; women = 822; studies = 3; $I^2 = 0\%$; [Analysis 6.2](#); moderate-quality evidence)

3. Proportion of women exclusively BF at six months (RR 1.07, 95% CI 0.87 to 1.30; women = 2161; studies = 4; $I^2 = 0\%$; [Analysis 6.3](#); moderate-quality evidence)

4. Proportion of women any BF at three months (average RR 0.98, 95% CI 0.82 to 1.18; women = 654; studies = 2; $I^2 = 60\%$; [Analysis 6.4](#); low-quality evidence)

5. Proportion of women any BF at six months (average RR 1.05, 95% CI 0.90 to 1.23; women = 1636; studies = 4; $I^2 = 61\%$; [Analysis 6.5](#); high-quality evidence)

6. Breastfeeding problems ([Duffy 1997](#) (n = 70) reported no group differences for mastitis, but less nipple pain and less nipple trauma for women who had a lactation consultant. [Kronborg 2012](#) (n = 1162) reported no group differences as to whether women responded 'yes' when asked about BF problems; [Analysis 1.9](#); [Analysis 1.10](#); [Analysis 1.11](#); [Analysis 1.8](#); moderate-quality evidence)

Sensitivity analysis

For the outcomes included in our 'Summary of findings', there were no trials assessed to be of high risk of bias for allocation concealment. We did not, therefore, conduct sensitivity analysis based on removing trials of high risk of bias.

Subgroup analysis

There were insufficient trials reporting outcome data by maternal education or occupation for us to conduct this analysis. For type of intervention, all of the first five comparisons of this review displayed the type of intervention in forest plots. There were too few trials in each subgroup to compare the groups in a meaningful analysis. For this update, due to time constraints, we have not conducted subgroup analysis by trial setting.

DISCUSSION

Summary of main results

In this update we have included 24 studies with 10,056 women. Twenty studies involving 9789 women contributed data to the analyses. There was no evidence that antenatal breastfeeding (BF)

education of any sort could improve the initiation of BF, the proportion of women with any BF and exclusive BF at three or six months as well as duration of BF over the standard care. However, It is important to mention here that of the 20 studies contributing data to this review, 13 had BF education or support as part of the standard care comparator. We have presented cluster trials with adjusted odds ratios separately in comparisons 4 and 5; most cluster trials did not contribute to the pooled effects in [Summary of findings for the main comparison](#).

Overall completeness and applicability of evidence

Twenty-two out of 24 studies were from high-income countries, mainly the USA, Australia, Canada and the UK. The only two included studies not from a high-income country were from Nigeria and Iran. Applying the results to low- and middle-income countries should be done cautiously. Although we have 24 included studies, there were diverse interventions among these studies. The overall completeness of evidence in this review is therefore too limited to make any strong conclusions or generalisations.

Quality of the evidence

For the comparison BF education versus standard care, we assessed five outcomes according to GRADE methodology. We did not downgrade any trial for lack of blinding, and no included trial had adequate blinding of participants or staff. We did not downgrade for substantial heterogeneity, though we have noted this on the 'Summary of findings' (SoF) table. Evidence for two outcomes was of high quality (initiation rate of BF and proportion of women with any BF at six months). A grade of high quality suggests confidence that the result is robust to future studies. Future trials should also find that antenatal education does not appear to improve uptake of BF or BF at six months. We assessed evidence for two further outcomes as of moderate quality, suggesting some doubt about the robustness of the observed effect due to small sample size in one analysis (proportion of women exclusive BF at three months) and a wide confidence interval crossing the line of effect in another (proportion of women exclusive BF at six months). Future studies may improve our understanding of the impact of antenatal education on exclusive BF at these time points. Lastly, we assessed evidence for the outcome of proportion of women with any BF at three months as of low quality, having the most uncertainty. Please see [Summary of findings for the main comparison](#) for further details.

Potential biases in the review process

We strictly followed the review process recommended by Cochrane ([Higgins 2011c](#)). We obtained all relevant studies identified from

search results. We independently reviewed all potentially relevant studies and resolved disagreement by discussion. Potential bias in the review process should be minimal.

Agreements and disagreements with other studies or reviews

A systematic review of professional support interventions for BF concluded that interventions expanding from pregnancy to the intrapartum period and throughout the postnatal period were more effective than interventions concentrating on a shorter period. In addition, intervention packages using various methods of education and support from well-trained professionals are more effective than interventions concentrating on a single method ([Hannula 2008](#)). However, this review included not only educational but also support interventions and did not restrict the included studies to randomised controlled trials.

Another Cochrane Review found that health education and peer support interventions can result in some improvements in the number of women beginning to breastfeed ([Dyson 2005](#)). This review is currently being updated ([Dyson 2005](#)). We were unable to confirm if peer counselling was significantly better than formal BF education for initiation of BF due to small single trials in our subgroups.

AUTHORS' CONCLUSIONS

Implications for practice

There was not enough evidence to suggest that any antenatal BF education was more effective than standard care or any other BF education method for improving BF initiation, any BF or exclusive BF at three or six months and BF duration.

Implications for research

There is an urgent need to conduct a high-quality, randomised controlled study with an adequate sample size and that is free from commercial influence to evaluate the effectiveness and adverse effects of antenatal BF education, especially in low- and middle-income countries where BF should have a more significant impact. It is recommended that such trials initially test the effect of individual interventions against no BF educational interventions. The no educational interventions group could be defined as no breastfeeding information or any breastfeeding information that is given in a non-formal and non-standardised way during the course of normal antenatal care consultation and would not involve any formal methods such as videos, written materials, a specific curriculum, involvement of fathers or a consultation with a lactation consultant or peer counsellor. The intervention and standard care provided in the no interventions group should be

described in detail. Outcomes should include the duration of any and exclusive breastfeeding and the proportion with any or exclusive breastfeeding at 3 or 4 and 6 months as well as adverse breastfeeding outcomes such as engorgement and adverse neonatal and infant outcomes such as sepsis and respiratory infections.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Duffy 1997

Methods	RCT. Using a sealed envelope containing group allocation in blocks of 12, with 6 in the control and 6 in the experimental group. Random assignment was carried out by the lactation consultant giving the educational session.	
Participants	Number of women randomised: 75 Inclusion criteria Attended antenatal classes in the study hospital, and intended to BF Verbal and written explanation was given Explained the completely voluntary and confidential nature of the study Exclusion criteria Delivered less than 37 weeks With medical complications	
Interventions	Experimental group (n = 37) An additional 1-h teaching session for nulliparas more than 36 weeks pregnant. The teaching intervention was through a lactation consultant, not involved in the data collection. The content of the teaching session was correct positioning and attachment of the baby on the breast for feeding Control group (n = 38) Standard educational programme of the study hospital	
Outcomes	Outcome measures (dichotomous) Primary 1. Incidence of BF at 6 weeks postpartum Secondary 1. Mastitis Outcome measures (continuous) Primary 1. LATCH score Secondary 1. Nipple pain (VAS) 2. Nipple trauma (NTI score)	
Notes	Loss of participants to follow-up: < 10% Blinding: outcome assessors This study was conducted in Western Australia	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described

Duffy 1997 (Continued)

Allocation concealment (selection bias)	Unclear risk	Sealed envelope (not described whether it was opaque or not)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details available
Selective reporting (reporting bias)	Unclear risk	No information
Other bias	Low risk	No other obvious biases

Finch 2002

Methods	RCT	
Participants	Number of women randomised: 60 Inclusion criteria English speaking, pregnant, HIV negative women Exclusion criteria Not specified	
Interventions	Experimental group (n = 30) BF education by trained LC, incentive, instruction and discussion with handout Control group (n = 30) Prenatal educational regarding benefit and barriers to BF	
Outcomes	1. Duration of BF 2. Feeding intentions	
Notes	This study was conducted in New York, USA	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information available
Allocation concealment (selection bias)	Unclear risk	No information available

Finch 2002 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information available
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow-up in intervention group 36.7% (11/30), in control group 3.3% (1/30)
Selective reporting (reporting bias)	Unclear risk	No information available
Other bias	Low risk	No other obvious biases

Flax 2014

Methods	Cluster-RCT
Participants	Setting: microcredit meetings, Bauchi state, Nigeria, Africa 77 microcredit meeting groups with 461 pregnant women, aged 15-45 years, attending monthly microcredit meetings for 7-10 months 39 meeting groups including 229 women were randomised to receive the monthly group BF learning sessions 38 meeting groups including 232 women were randomised to receive standard microcredit group meeting with no BF learning sessions
Interventions	Experimental group (229 women) Monthly group BF learning sessions including weekly cell phone BF text and voice messages to cell phone provided to each small microcredit group and monthly face-to-face BF information during microcredit monthly meeting. Information given included: exclusive BF to 6 months; initiation of BF within 1 h of birth; giving only breast milk not fluids during the first 3 days of life for 7-10 months The messages were generated via songs and dramas by participants Adult learning techniques and participatory principles used with 1-3 key messages each session including counselling cards for the intervention Control group (232 women) Women in the control clusters received only standard microcredit group meeting with no BF interventions
Outcomes	1. Exclusive BF to 1, 3, and 6 months 2. Initiation of BF within 1 h of delivery 3. Use of only colostrum or breast milk during the first 3 d of life
Notes	
<i>Risk of bias</i>	

Flax 2014 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Block randomisation, process not described, other than it happened at the level of the monthly community meeting (clusters)
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not described, but highly unlikely that blinding was possible
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Baseline and final survey interviews were conducted by an independent team of trained data collectors unaware of the clients' study arm assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Eligible clients (n = 229 intervention, n = 232 control) were in the randomised meeting groups. At follow-up, 196 (86%) and 194 (84%) clients remained in the intervention and control arms, respectively
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes were published and reported on
Other bias	Low risk	No other obvious biases

Forster 2004

Methods	RCT Random allocation to a control group or 1 or 2 intervention groups, randomised by an external computerised system accessed by telephone by a research midwife
Participants	Number of women randomised: 984 Inclusion criteria Women booked as public patients. Women who were primiparas. Women pregnant between 16 and 24 weeks. Women able to read and write in English Exclusion criteria Women with physical problems that prevented BF. Women who chose private obstetric care. Women choosing to give birth at birth centre
Interventions	Experimental group Group 1 (n = 327): 1.5-h session on practical BF using teaching aids. Latch-on technique demonstrated with dolls and knitted breasts, also BF complications and management. Plus access standard care available Group 2 (n = 329): two 1-h sessions that focused on changing attitudes to BF. Women were encouraged to bring their partners or a significant other. Session 1 included information about BF advantages, views and attitudes of participants, their friends and families and society. For session 2, participants were encouraged to interview their own mother or her partner's mother about attitudes of BF, which then was reflected and discussed in this session. Access standard care available

	Control group (n = 328) Able to access standard care, which included formal BF education sessions etc	
Outcomes	Duration of any BF at 2-4 d, excluded babies not yet feeding. Duration of exclusive BF at 2-4 days, excluded babies yet not feeding Number of mothers any BF at 6 months Number of mothers exclusive BF at 6 months	
Notes	Loss of participants to follow-up and reasons: < 10% Blinding: unclear Intention-to-treat analysis: used Each intervention group was compared only with the group of women allocated to standard care; they were not compared with each other For this review we have presented separate intervention groups in Comparison 1; where we have totals in the analysis in Comparison 6 we have split the control group between the intervention arms Study was conducted in Melbourne, Australia	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computerized system of biased urn randomisation was accessed by telephone by the research midwife to ascertain women's group allocation."
Allocation concealment (selection bias)	Low risk	"A computerized system of biased urn randomisation was accessed by telephone by the research midwife to ascertain women's group allocation."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not described, but very unlikely to be blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	The follow-up rate in practical skill, attitudes, standard care we re 91%, 90% and 91%, respectively
Selective reporting (reporting bias)	Unclear risk	No information available
Other bias	Low risk	No other obvious biases

Kaplowitz 1983

Methods	RCT
Participants	44 consecutive women from 2 upstate New York Women, Infants and Children (WIC) programmes, at least 18 years old, in 4th to 6th month of pregnancy, primigravida or women who had bottle-fed previous children or who previously had an unsuccessful BF experience were randomly assigned to experimental (21 women) or control (23 women) groups
Interventions	Experimental group (21 women) 5 pamphlets providing information on the benefits of BF, basic physiology of lactation, proper nursing technique were mailed to the women's homes 1 at a time over 5 consecutive weeks Control group (23 women) Did not receive pamphlets
Outcomes	1. Women's knowledge about nursing after the intervention 2. Attitude toward BF before and after the intervention These outcomes were not relevant to the review objective.
Notes	This study was conducted in New York. No information about BF practice available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not described, but unlikely to be blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	No information available
Other bias	Unclear risk	Inadequate information

Methods	RCT	
Participants	Setting: At 4 participating prenatal clinics between the University of Virginia (UVA) Health System and the Virginia Commonwealth University (VCU) Health System, Virginia in the USA from 2009 to 2012 Inclusion criteria Pregnant women of 24-41 weeks' gestation who were WIC-eligible (income of 185% or less of the federal poverty income guidelines) Exclusion criteria Women with multiple-gestation pregnancy, any known contraindication to BF (e.g. HIV infection, drug use, or receipt of chemotherapy), or their primary language was not English Total numbers of 522 eligible pregnant women were enrolled (459 at UVA, 63 at VCU) . No information of how many randomised women of each group was reported	
Interventions	Experimental group A 25-min educational BF video (<i>Better Breastfeeding</i>, Injoy Productions, 2008) provided general information about BF, including importance, latch, hunger cues, positioning, sore nipples, engorgement, how breast milk is made, and lifestyle issues Total number analysed: 249 Control/Comparison intervention A 20-min educational video about nutrition during pregnancy (<i>Healthy Pregnancy Nutrition</i>, Injoy Productions, 2007). It covered topics including healthy diet and the importance of exercise during pregnancy Total number analysed: 248	
Outcomes	Breastfeeding initiation Time of first feeding Any infant complication (hypoglycaemia, rule-out sepsis, hypothermia, transient tachypnoea of the newborn, other breathing problems, cardiac problem, hyperbilirubinaemia, and others.) Unlikely to be related to the intervention. Also for maternal complications Infant length of stay in newborn nursery only and never NICU and/or intermediate care Nursery (ICN)	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated block randomisation sequence using random block sizes, stratified by prenatal clinic, was used
Allocation concealment (selection bias)	Low risk	One member of the study team with no direct contact with participants prepared all of the consecutively-numbered, sealed, opaque envelopes, which the research assistant opened just prior to loading the video for the participant to view

Kellams 2016 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not described, but highly unlikely that blinding was possible
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Research assistants abstracting data were blinded to the group to which the participant was assigned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Eligible women were 1580, 522 were randomised but there was no information of assigned number to each group. Analysis was done in 497 women (249 in intervention and 248 in control) account for 95% of the randomised women However, BF outcomes were analysed in 346 (70%; 174/249 for intervention and 69%; 172/248 for control) These were only those who gave BF
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes were published and reported on.
Other bias	Low risk	No other obvious biases

Kistin 1990

Methods	RCT Women in Monday clinic were randomised with a random number table into 2 intervention groups Friday clinic became control group (not randomised, therefore data could not be used, both intervention groups data could be compared, as they were randomised)
Participants	Number of women randomised: 74 Inclusion criteria Women 24 weeks' gestation or less Black women born in the USA Exclusion criteria None mentioned
Interventions	2 types of prenatal education. Individual BF and antenatal BF class Experimental groups Intervention group 1 (38 women): antenatal group BF class, 50-80 min, at least 1 session discussing myths, problems and benefits of BF Intervention group 2 (36 women): individual pre-counselling with a nurse practitioner or paediatrician, one-to-one, 15-30 minutes, between 30-40 weeks' gestation, similar topics discussed in IG1 Control group Normal antenatal care. No additional information but not randomised, therefore data were excluded, and not included in our analysis
Outcomes	1. Duration of any BF 2 weeks 2. Duration of any BF 6 weeks

Kistin 1990 (Continued)

	3. Any BF at 3 months	
Notes	Loss of participants to follow-up: 18.2% Blinding: participants; no, counsellors; not feasible, outcome assessors; not clear Intention-to-treat analysis: not clear This study was conducted in Chicago, USA	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers was used
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not described, but highly unlikely
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not enough information
Selective reporting (reporting bias)	Unclear risk	Information not available
Other bias	Low risk	No other obvious biases

Kluka 2004

Methods	RCT
Participants	Number of women randomised: 209 Inclusion criteria Primiparous women who were planning to BF their infants. Exclusion criteria None mentioned
Interventions	Experimental group: 111 women Usual care plus a self-assessment pre-workshop guide and an interactive, educational, antenatal workshop Control group: 98 women Usual care
Outcomes	BF at 3 and 6 months

Kluka 2004 (Continued)

Notes	This study was conducted in Canada	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comparable loss to follow-up (< 20% at 6 months in both arms)
Selective reporting (reporting bias)	Unclear risk	No information available
Other bias	Low risk	No other obvious biases

Kools 2005

Methods	Cluster randomisation of 10 home healthcare centres. Coin flip determined which centres would receive intervention Clusters had comparable overall pre-randomisation rates and sizes
Participants	Number of women randomised: 781 Inclusion criteria Women considering BF All pregnant women using the identified 3 home healthcare organisations and from their 10 centres Women pregnant in their 7th month of pregnancy Exclusion criteria Women with babies weighing < 2000 g
Interventions	Experimental group 408 women received standard care and BF booklet, which was used and referred to by caregiver at each consultation (which included practical instructions on BF, discussion around how to cope with BF, motivational discussion to initiate and maintain BF and additional information if asked for). Opportunity to access 24-hour free lactation consultant Control group

Kools 2005 (Continued)

	373 received standard antenatal care and BF booklet and phone number for BF questions or BF problems	
Outcomes	1. Number of mothers any BF at birth 2. Number of mothers BF exclusively at birth 3. Number of mothers any BF at 3 months 4. Number of mothers exclusive BF at 3 months	
Notes	Loss of participants to follow-up: < 10% Blinding: participants; no, others unclear Intention-to-treat analysis: used This study was conducted in Maastricht, Netherlands	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Coin flip
Allocation concealment (selection bias)	Unclear risk	Coin flip was used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not described.Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not described. Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal loss to follow-up in experimental group and no loss to follow-up in control group
Selective reporting (reporting bias)	Unclear risk	No information available
Other bias	Low risk	No other obvious biases

Kronborg 2012

Methods	RCT
Participants	Number of women randomised: 1193 Inclusion criteria 1193 nulliparous women were recruited before week 21 + 6 days of gestation, 603 were randomised to the intervention group, and 590 to the reference group. The inclusion criteria were nullipara registered at the Aarhus Midwifery Clinic, older than 18 years of age at enrolment, with a singleton pregnancy, and the ability to speak and understand

Kronborg 2012 (Continued)

	Danish	
Interventions	Experimental group Structured antenatal training programme for 9 h attended in mid-pregnancy Control group Usual practice (no antenatal training)	
Outcomes	1. Initiation of BF 2. BF at 6 weeks and 1 year	
Notes	This study was conducted in Denmark	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was assigned by one staff midwife using computer voice response system. Randomisation was through an algorithm generated by a data manager. Ratio of 1:1."
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not described, not possible
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Postnatal midwives (personnel) were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	16 out of 603 and 15 out of 590 women in the intervention and reference groups were lost to follow-up respectively
Selective reporting (reporting bias)	Low risk	Reported all outcomes as presented in methods
Other bias	Low risk	Baseline characteristics were quite comparable between intervention and reference groups. No other obvious biases

Lavender 2005

Methods	Cluster-RCT Unit of randomisation: 8 electoral wards in 1 county, pairs were matched according to Jarman Underprivileged area score (UPA) Within-pair randomised = 4 clusters each Opaque sealed envelopes

Participants	Number of women randomised: 1312 Inclusion criteria Women registered with a practice site/GP in one of the 8 electoral wards Women who expressed a desire to BF Women with no detected foetal abnormality at 20-week ultrasound Exclusion criteria Women with detected foetal abnormality Women who gave birth before 36 weeks' gestation Women who lived in potentially unsafe homes Women who planned to bottle feed Women who had previously BF for at least 6 weeks	
Interventions	1 antenatal BF education session with the woman's attending community midwife. Midwives were trained for this intervention Experimental group (n = 633) Normal antenatal care plus during third trimester attendance of a single antenatal BF education session. Each session involved up to 8 women and was facilitated by a qualified infant feeding co-ordinator Control group (n = 679) Received standard antenatal care that included BF advice from attending clinic midwives	
Outcomes	1. Number of mothers any BF at hospital discharge 2. Number of mothers any BF at 2 weeks 3. Number of mothers any BF at 4 weeks 4. Number of mothers any BF at 6 weeks 5. Number of mothers any BF at 4 months 6. Number of mothers exclusive BF at 4 months 7. Number of mothers any BF at 6 months 8. Number of mothers any BF at 12 months	
Notes	Loss of participants to follow-up: < 10% Blinding: participants: not feasible, counsellors: no, outcome assessors: yes Intention-to-treat analysis: used This study was conducted in northwest UK	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes were used
Blinding of participants and personnel (performance bias) All outcomes	High risk	The intervention was not feasible to be blinded

Lavender 2005 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up < 10% in both arms
Selective reporting (reporting bias)	Unclear risk	No information available
Other bias	Low risk	No other obvious biases

MacArthur 2009

Methods	Cluster-RCT
Participants	66 antenatal clinics with 2511 pregnant women 33 clinics including 1140 women were randomised to receive the peer support worker service 33 clinics including 1371 women were randomised to receive standard care
Interventions	Intervention group (1140 women) An antenatal peer support worker service planning a minimum of 2 contacts with women to provide advice, information, and support from approximately 24 weeks' gestation within the antenatal clinic or at home. The trained peer support workers were of similar ethnic and socio-demographic backgrounds to their clinic population Control group (1371 women) Women in the control clusters received standard antenatal care, which included usual information and advice from midwives on BF without input from community peer support workers
Outcomes	Initiation of BF obtained from computerised maternity records of the hospitals where women from the primary care trust delivered
Notes	This study was conducted in Birmingham, UK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	The intervention was not feasible to be blinded

MacArthur 2009 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data on outcome were supplied to the research team in an anonymous format
Incomplete outcome data (attrition bias) All outcomes	Low risk	113 out of 2511 women (4.5%) who participated in the trial were not available for primary outcome assessment
Selective reporting (reporting bias)	Unclear risk	No information available
Other bias	Low risk	No other obvious biases

Mattar 2007

Methods	Cluster-RCT A computer-generated list was used to randomise the women into the 3 groups. Each woman was allocated to the intervention group next on the list after written informed consent had been obtained. Singapore
Participants	Number of women randomised: 401 Inclusion criteria Singleton pregnancy, gestation of at least 36 weeks at recruitment, no uterine scar, and the absence of any obstetric complication that would contraindicate vaginal delivery, with informed consent Exclusion criteria Not described
Interventions	Multiple versus single Experimental group Group A (n = 123): received an information booklet describing the techniques and benefits of BF, which was written and published by the hospital's BF support group. It contained practical advice on feeding techniques, expressing breast milk, and management of common BF problems. Participants also watched a 16-min educational video entitled "14 Steps to Better BF" (InJoy Videos, Boulder, CO), in which the benefits of BF were introduced, correct positioning, latch-on, and breast care were demonstrated, and common concerns (such as nipple pain) discussed. In addition, each woman had one 15-minute session with a lactation counsellor who examined the woman's nipples to assess adequacy for BF and answered questions on BF Group B (n = 132) received the same booklet and watched the same video but did not have an individual session with the lactation counsellor Control group Group C (n = 146) Did not watch the video, and did not have counselling. The primary report stated that the control group did not receive the booklet, video or counselling (Mattar 2007 p. 74) All women in all randomised groups had standard care during pregnancy, including access to postnatal BF support
Outcomes	1. Number of mothers BF at 3 months 2. Number of mothers BF at 6 months

Mattar 2007 (Continued)

Notes	Loss of participants to follow-up: 10% Blinding: only outcome assessor Intention-to-treat analysis addressed: yes This study was conducted in Singapore Comparison 4 includes the 2 treatment arms A and B	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list
Allocation concealment (selection bias)	Low risk	Each woman was allocated to the intervention group next on the list after written informed consent had been obtained
Blinding of participants and personnel (performance bias) All outcomes	High risk	The intervention was not feasible to be blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up 10%
Selective reporting (reporting bias)	Unclear risk	Information not available
Other bias	Low risk	No other obvious biases

Noel-Weiss 2006

Methods	RCT
Participants	Number of women randomised: 101 inclusion criteria Nulliparous women expecting a single child, an uncomplicated birth, and planning to BF The women had to read and write in English and have a telephone to complete the postpartum questionnaires. To remain in the study, a mother and her infant had to be discharged at the same time and be able to BF without restriction Exclusion criteria Not described
Interventions	Workshop Experimental group (n = 47) Standard care plus a 2.5-h prenatal BF workshop designed using Bandura's theory of

Noel-Weiss 2006 (Continued)

	self-efficacy and adult learning principles. The intervention involved the use of lifelike dolls, videos, and discussion in a comfortable atmosphere Control group (n = 45) Standard care	
Outcomes	1. Maternal BF self-efficacy 2. BF duration measured at 4 weeks and 8 weeks postpartum	
Notes	This study was conducted in Ontario, Canada	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Low risk	Used sealed, sequentially numbered, opaque envelope containing a slip of paper stating either Control or Workshop
Blinding of participants and personnel (performance bias) All outcomes	High risk	The intervention was not feasible to be blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only outcome evaluators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysed the data with both the intention-to-treat assumption and using the actual workshop attendance. 101 randomised and 92 were available for analysis
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Low risk	No other obvious biases

Olenick 2010

Methods	RCT
Participants	Number of women randomised: 182 Inclusion criteria Pregnant women enrolled for prenatal care at 24 weeks (or beyond) who consented to participate Exclusion criteria Age < 18 years, stated intention to bottle-feed with formula, non-English speaking, those for whom BF was medically contraindicated, those whose newborns would be anticipated to be incapable of BF, no access to telephone for follow-up and those who were not planning to keep or raise their baby

Olenick 2010 (Continued)

Interventions	Experimental group 2-h BF self-efficacy theory-based class (86 women) Control group No class (96 women)	
Outcomes	1. BF duration 2. BF exclusivity and confidence through 12 weeks	
Notes	This trial was conducted in Texas, USA.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote "A research assistant was used for all postpartum data collection by phone. Although she did have access to the information regarding the subjects' group assignment, she did not refer to this information when doing the phone interviews, in effect blinding her to their status. In this way, there was greater objectivity both by the interviewer and the interviewee."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote "The overall dropout rate was 7.7%."
Selective reporting (reporting bias)	Unclear risk	No information available
Other bias	Low risk	No obvious baseline differences and other biases

Pate 2009

Methods	RCT in parallel arms
Participants	Setting: Arkansas department of Health USA Inclusion criteria Primiparous pregnant women on WIC with an expected due date greater than 2 months post-enrolment, ages of 20 and 30, have access to email and the Internet and provide written consent to participate to completion Exclusion Criteria

	Women identified as substance abusers on their ADH WIC-5 record, received WIC in counties served by BF peer counsellors and BF contraindicated for any of the following reasons: 1. takes street drugs or does not control alcohol use; 2. has an infant with galactosaemia; 3. has human immunodeficiency virus (HIV) infection; 4. has active, untreated tuberculosis; 5. takes certain medications that are contraindicated for BF; 6. currently undergoing treatment for breast cancer. 145 pregnant women on WIC were screened by Health Department nutritionists for eligibility and willingness to participate in the study. 23 participants completed consent and pre-test forms, were randomly assigned to groups, and participated in the study	
Interventions	Experimental group 6 weeks of peer counsellor-guided web-based education and support related to BF practices. In addition, the usual care of nursing and nutrition visits at the health department local health unit and written materials per Arkansas Department of Health (ADH) policy and procedure guidelines were given to the participants Control group Usual care consisted of non-web-based interventions, such as face-to-face counselling and education and the distribution of written materials	
Outcomes	Breastfeeding self-efficacy None of our pre-specified outcomes were reported	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible subjects were randomly assigned to either the intervention group or the control group using a computer-generated 2-block random number generator in a 1:1 ratio
Allocation concealment (selection bias)	Unclear risk	As above
Blinding of participants and personnel (performance bias) All outcomes	High risk	Intervention could not be blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data on all participants who were randomly assigned was analysed in the groups to which they were allocated on an intention-to-treat basis

Selective reporting (reporting bias)	Low risk	Pre-specified outcomes were published and reported
Other bias	Unclear risk	No information available

Raeisi 2014

Methods	Single-centre RCT
Participants	100 pregnant women and their partners randomised Inclusion criteria Women in the second trimester of pregnancy with no underlying disease or pregnancy complication Exclusion criteria No details given
Interventions	Intervention group The case group was provided with an educational package on promoting fathers' participation. They attended 3 training sessions where they were trained by brochures Control group Given no intervention
Outcomes	1. Birth weight 2. Weight gain during the first 6 months 3. Jaundice 4. Duration of BF 5. Spouse's level of awareness
Notes	Trial conducted at family health research centre in Tehran, Iran

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed according to the table of random numbers."
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not described but very unlikely to be blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results presented as text (no tables) but appears all data for all participants reported

Raeisi 2014 (Continued)

Selective reporting (reporting bias)	Low risk	All outcomes reported and published
Other bias	Low risk	No other obvious biases

Rossiter 1994

Methods	RCT, did not describe how randomisation was done	
Participants	Number of women randomised: convenience sample of 194 pregnant women Inclusion criteria 1. Ethnic Vietnamese or other women who were born and reared in Vietnam. 2. Vietnamese speaking 3. At least 12 weeks pregnant 4. Gave consent to participate Exclusion criteria Unforeseen circumstances (miscarriage, stillbirth, change of address)	
Interventions	Culture and language-specific educational programme Experimental group A 25-min videotape programme followed by a series of 3 x 2 h of small group discussion sessions conducted in Vietnamese Control group BF and childbirth pamphlets	
Outcomes	1. Number of mothers BF at birth 2. Number of mothers BF at 4 weeks 3. Number of mothers BF at 6 months	
Notes	Loss of participants to follow-up: < 10% Blinding: Participant: not feasible Clinician: unclear Outcome assessor: unclear Intention-to-treat analysis: unclear This study was conducted in Sydney, Australia.	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not described but highly unlikely to be blinded

Rossiter 1994 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up < 10% in both arms
Selective reporting (reporting bias)	Unclear risk	Information not available
Other bias	Low risk	No other obvious biases

Ryser 2004

Methods	RCT
Participants	Total number of women randomised: 54 Pregnant women, at least 18 years old, English speaking, able to read and write, received prenatal care and could attend 4 visits before delivery, low income, having access to telephone, undecided about BF method during initial contact with researchers
Interventions	Intervention group (26 women) Educational program (Best Start) included: 1. counselling session 2. viewing video 3. written materials addressing common BF barriers perceived by low-income women Control group (28 women) No exposure to the programme
Outcomes	1. Attitude toward BF 2. Social and professional support 3. BF sense of control 4. Intention to BF 5. BF at 7 days delivery
Notes	This study was conducted in Houston, Texas, USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Women selected a sealed envelope. No information about envelopes

Ryser 2004 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not described, unlikely to be blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol was available
Other bias	Low risk	No other obvious biases

Schlickau 2005a

Methods	RCT. Method of randomisation was not described
Participants	Number of women randomised: 30 Inclusion criteria Low-risk primigravida, Hispanic, in their third trimester, received care at Sedgwick, not planning to work outside the home for 6 months Exclusion criteria Not described
Interventions	Prenatal BF education Experimental group Level 1: the researcher approached the expectant mother. All participants confirmed that they planned to BF. Contents included benefits of BF. Charts and pictures were used to present supply-and-demand concept and prenatal breast preparation. Early and consistent BF practices were emphasised. A doll was used as a model for instruction about holding and positioning the baby and BF discreetly Level 2: completed first level. Participants were introduced the concept of “baby quarantine” (nothing enters the baby’s mouth except the mother’s breast for at least 40 days after birth. The benefits of avoiding bottles, pacifier and supplementation to promote establishment of milk for successful BF were reinforced. BF commitment was encouraged through the use of checklist Control group Standard care offered advice to BF and handouts were distributed during the initial prenatal visit
Outcomes	1. Number of mothers BF at 45 days 2. Duration of any BF
Notes	Loss of participants to follow-up: 17%. This study was conducted in Kansas, USA. Schlickau 2005b is a thesis which included three parts: Part 1) Qualitative study

[Schlickau 2005a](#) (Continued)

	Part 2) Multiple arm study of 30 women with a control group, a BF workshop (level 1) , and a BF workshop with introduction to concept of 'baby quarantine' (level 2). Part 2 is reported in Schlickau 2005a Part 3) 86 women randomised to either control or BF education workshop Part 3 results are presented under Schlickau 2005b . Part 2 results are presented under Schlickau 2005a .	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not described but unlikely to be blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss of participants to follow-up: 17%
Selective reporting (reporting bias)	Unclear risk	No information available
Other bias	Unclear risk	Not enough information

[Schlickau 2005b](#)

Methods	RCT
Participants	Number of women randomised: 86 Inclusion criteria Primigravida, immigrant Hispanic women aged 15-45 , 32-36 weeks' gestation, stable family situation, had a work situation compatible with BF for 6 weeks, had normal nipple assessment Exclusion criteria Homeless, not in a temporary agencies or shelter, high-risk pregnancies, serious illness of the newborn or mother that precluded BF, stillbirth, unforeseen family situation
Interventions	Prenatal BF education Experimental group (44) BF education workshop Control group (42) Standard care

Schlickau 2005b (Continued)

Outcomes	1. Initiation of BF 2. Duration of any BF
Notes	This study was conducted in Kansas, USA. Schlickau 2005b is a thesis which included three parts: Part 1) Qualitative study Part 2) Multiple arm study of 30 women with a control group, a BF workshop (level 1) , and a BF workshop with introduction to concept of 'baby quarantine' (level 2). Part 2 is reported in Schlickau 2005a Part 3) 86 women randomised to either control or BF education workshop Part 3 results are presented under Schlickau 2005b . Part 2 results are presented under Schlickau 2005a .

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Manila packet sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not described but unlikely to be blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up in intervention group (9.1%, 2/44), in control group (9.5 %, 4/42)
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Low risk	No other obvious biases

Serwint 1996

Methods	RCT. Random number table was used. Method of randomisation (allocation) was not described
Participants	Number of women randomised: 156 Nulliparous women, 18 years or older, with a foetus of gestational age of 28 weeks or less, who had not yet selected a paediatrician or wanted their infants to receive paediatric care at the hospital-based paediatric clinic
Interventions	LC plus standard BF education (81 women) versus standard BF education (75 women)

Serwint 1996 (Continued)

Outcomes	1. Number of mothers who initiated BF at birth 2. Number of mothers BF at 30 days 3. Number of mothers BF at 60 days	
Notes	This study was conducted in Baltimore, USA	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table was used
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not described but unlikely to be blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up 7.7%
Selective reporting (reporting bias)	Unclear risk	No information available
Other bias	Low risk	No other obvious biases

Wolfberg 2004

Methods	RCT. Method of randomisation was not described
Participants	Number randomised: not clear (59 couples completed study) 567 expectant mothers were approached during 1st and 2nd trimester, refused to participate 24%; lost during prenatal period 36%; lack of involvement with father 8%; fathers refusal to participate 11%; fathers' failure after enrolling 9%, completed the study with 59 couples Inclusion criteria Women who sought prenatal care in the resident and faculty practices at Johns Hopkins Hospital Exclusion criteria Not described
Interventions	Classroom discussion on infant care and BF for expectant fathers Experimental group (27 fathers) Groups of 4-12 expectant fathers attending the classroom with open discussion about BF

	and support each other to be advocates for BF among fathers in the groups, facilitated by a man who was himself a father. 2-h classes used a variety of teaching media were held approximately every 2 weeks Control group (32 fathers) The class covered topics related to infant care and safety only using the same facilitator, and methods of interactive and informal education as of those the intervention group. These subjects did not receive the intervention class that contained the BF content
Outcomes	1. Number of mothers for initiated BF 2. Number of mothers BF at 4 weeks 3. Number of mothers BF at 6 weeks 4. Number of mothers BF at 8 weeks
Notes	Loss of participants to follow-up: 36% Blinding: Participant: not feasible Clinician: unclear Outcome assessor: unclear Intention-to-treat analysis: not used This study was conducted in Baltimore, USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not described but unlikely to be blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow-up 36%
Selective reporting (reporting bias)	Unclear risk	No information available
Other bias	Low risk	No other obvious biases

Methods	RCT	
Participants	Setting: 2 study hospitals based on the geographic representativeness and high volume of eligible mothers in Hong Kong Inclusion criteria: pregnant women with 1) 18 years of age or older; 2) Cantonese-speaking; 3) primiparous; 4) at least 35 weeks of gestation; 5) a singleton pregnancy; 6) no serious medical or obstetric complications; 7) intending to breastfeed; and 8) planning to stay in Hong Kong for at least 6 months after delivery Exclusion criteria: being not entitled to health benefits in Hong Kong, not a Hong Kong resident, or both Recruitment period: Jan-June 2013 Follow-up completed: Dec 2013 Total numbers of 469 eligible pregnant women were enrolled and randomised (233 to intervention and 236 to standard care)	
Interventions	Experimental group (233 women) Standard care plus one-to-one (20-30 min) BF education and support session based on WHO guideline for baby-friendly hospitals and evidence-based maternity care. The intervention was given immediately after randomisation in a private room in the antenatal clinics to minimise contamination between the two treatment groups Control group (236 women) Standard antenatal care: standard maternal and foetal health checks by either clinic midwives or obstetricians along with health education to promote a healthy pregnancy	
Outcomes	Exclusive BF at 6 weeks, 3 and 6 months postpartum. Overall duration of any and exclusive BF (age in weeks when the infant first ingested formula and ceased BF completely, respectively) across the first 6 months postpartum	
Notes	This study was conducted in Hong Kong.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An independent researcher who did not participate in participant recruitment or data collection generated the allocation sequence using the statistical software Stata13.1
Allocation concealment (selection bias)	Low risk	Allocation sequences were kept in sequentially numbered, opaque, sealed envelopes. The research nurse opened up the next envelope in the sequence to determine the assigned group after a pregnant woman had agreed to participate and had signed the written consent form
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of the research nurse or the participants was not possible given the nature of the intervention

Wong 2014 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	The BF follow-up data were collected by a research assistant who was blinded to the participants' group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	443 (94.5% of 469), 222 (95.3% of 233) in intervention and 221 (93.6% of 236) in standard care, completed all follow-up to 6 months postpartum or until weaned
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes were published and reported on.
Other bias	Low risk	Comparable baseline characteristics between intervention and standard care groups presented

BF: breastfeeding

LC: lactation consultation

NTI: nipple trauma index

RCT: randomised controlled trial

VAS: visual analogue scale

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ahmad 2012	Not RCT
Aidam 2005	Not only antenatal BF education. 9 home visits were provided in the 6-month postpartum period
Anderson 2005	Not only antenatal BF education. Peer counsellors also gave postpartum visits
Barlow 2006	Not only antenatal BF education. Home visits extended to 6 months postpartum
Bonuck 2005	Not only antenatal BF education. Lactation consultants also made postpartum hospital or home visits
Bonuck 2013	Included both pre and postnatal interventions.
Brent 1995	Not only antenatal BF education. Lactation consultants provided support in the postpartum period and until infants up to 1 year of age
Caulfield 1998	Not only antenatal BF education. Peer counsellors followed up women in the postpartum period as long as they continued to breastfeed
Chapman 2004	Not only antenatal BF education. Peer counselling extended to postpartum period

(Continued)

Chapman 2013	Included both pre and postnatal interventions
Edwards 2013a	Not only antenatal BF education. Doula home visits extended to postpartum period
Edwards 2013b	Animated computer agent used prenatally during a third trimester office visit and perinatally at discharge from the hospital plus usual care. The perinatal dialogue, delivered in the hospital, focused on essential information that mothers need the most in their first 3 days of BF ("breastfeeding 101"). The perinatal dialogue also focused on addressing the most commonly asked questions by new BF mothers and motivating adherence to the CDC-recommended 6 months of exclusive BF goal
Ekstrom 2006	Not only antenatal BF education. Support was also provided at 3-day, 3-month and 9-month postpartum
Eneroth 2007	Not RCT, objective not relevant
Finch 2015	Not related to BF
Gijbbers 2006	Not only antenatal BF education; a home visit was also provided postnatally
Graffy 2004	Not only antenatal BF education. Lactation counsellors provided postnatal support by telephone or home visits
Grossman 1988	Not RCT (letter to editor commenting on non-RCT papers).
Hall 2007	Not RCT
Hanafi 2014	Not RCT
Howell 2014	Post-natal interventions
Isselmann 2006	Intervention was not antepartum BF education
Jahan 2013	Nutritional education not BF education
Jenner 1988	Not RCT
Johnston 2001	Not RCT
Kafatos 1991	Not only antenatal BF education. Home visits continued after delivery until the infant was 12 months
Kamau-Mbuthia 2013	Included pregnant and post-partum women and 3-month postpartum intervention
Kimani-Murage 2013	Not antenatal BF education (only protocol)
Kimani-Murage 2015	Included both pre and postnatal interventions (Only protocol)
Kupratakul 2010	Not only antenatal BF education. Document on BF was provided, that affects BF behaviour of postpartum mothers

(Continued)

Loh 1997	Not RCT
Mattar 2003	Not RCT (letter to editor with comments on non-RCT papers).
Memmott 2006	Not RCT
Moore 2007	Not RCT, did not evaluate antenatal BF education
Morrow 1999	Not only prenatal BF education intervention. Peer counsellors also visited mothers at 1st, 2nd, 4th and 8th week postpartum
Muirhead 2006	Not only prenatal BF education intervention. Peer supporters provided support up to 16 weeks postpartum
NCT01383070	Not only prenatal BF education intervention. Counseling during the antenatal period, at delivery and during the immunisation visits
Nekavand 2014	Postnatal education intervention
Ochola 2013a	Included postnatal intervention
Ochola 2013b	Not RCT
Otsuka 2014	Not RCT
Petrova 2009	Not only prenatal BF education intervention. Lactation consultant also provided support postnatally
Rea 1999	Participants were not pregnant women.
Redman 1995	Not only antenatal BF educational intervention. Lactation counsellors also visited women after delivery
Reeve 2004	Not RCT
Reifsnider 1997	Not RCT (systematic assignment)
Ross 1983	Not RCT
Sandy 2009	Not only antenatal BF education. Following the birth of a prenatally enrolled target child, the Family Support Workers (FSW) typically made a visit to the newborn's mother in the hospital. During this visit, the FSW assisted programme group mothers with any problems initiating BF. After hospital discharge, FSWs continued to offer programme group mothers information and support in the home on a weekly basis
Sciacca 1995	Not only antenatal BF education. BF incentives were given pre and postnatally
Spinelli 2013	Not RCT of antenatal BF education.
Srinivas 2015	Peer counsellor, the intervention was performed at pre and post delivery
Stockdale 2008	Included antenatal and postnatal interventions.

(Continued)

Stuebe 2016	Included antenatal and postnatal interventions.
Su 2007	Not only antenatal BF education. Lactation support was also provided in the postpartum period
Taddei 2000	Participants were not pregnant women. They were health professionals
Uauy 2013	Not yet recruited
Walkup 2009	Not only antenatal BF education. Paraprofessional delivered home visit education during the postpartum period
Waller 1946	Not RCT
Wambach 2009	Not only antenatal BF education. Lactation consultant and peer counselling extended through 4 weeks postpartum
Webb 2013	Included antenatal and postnatal interventions.
Wen 2011	Not antenatal BF education.
Westdahl 2008	Intervention was not antenatal BF education.
Westphal 1995	Participants were not pregnant women.
Wiles 1984	Not RCT
Wockel 2009	Participants were not pregnant women.

BF: breastfeeding

RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Bahri 2013

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting translation

Bastani 2009

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting translation

BF: breastfeeding

Characteristics of ongoing studies *[ordered by study ID]*

Maycock 2015

Trial name or title	A study to prolong BF duration: design and rationale of the Parent Infant Feeding Initiative (PIFI) randomised controlled trial
Methods	Four-arm, factorial randomised controlled trial of partners of pregnant women
Participants	Male partners of pregnant women
Interventions	Control group (CG) - usual care Medium intensity intervention 1 (MI1) - specialised antenatal classes for partners with supporting printed materials Medium intensity intervention 2 (MI2) - antenatal and postnatal social support delivered via smartphone application (exclude- involves postnatal intervention) High intensity intervention - specialised antenatal classes and antenatal and postnatal social support delivered via smartphone application (exclude- involves postnatal intervention)
Outcomes	Primary outcomes Duration of any BF Duration of exclusive BF Secondary outcomes Age of introduction of formula Age of introduction of complementary foods ('solids') Infant feeding attitudes of both partners. Maternal BF self-efficacy
Starting date	
Contact information	jane.scott@curtin.edu.au School of Public Health, Curtin University, GPO Box U1987, Perth 6845, Australia Collaboration for Evidence, Research and Impact in Public Health (CERIPH), Curtin University, Perth,

Maycock 2015 (Continued)

	Australia
Notes	

DATA AND ANALYSES

Comparison 1. One type of BF education versus standard/routine care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of any breastfeeding	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 BF education session versus standard care (weeks)	1	165	Mean Difference (IV, Fixed, 95% CI)	0.0 [-2.78, 2.78]
1.2 BF education session versus standard care (days)	1	16	Mean Difference (IV, Fixed, 95% CI)	6.20 [-10.84, 23.24]
2 Any breastfeeding at 3 months	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 BF education workshop versus standard care	1	185	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.92, 1.24]
2.2 BF education session versus standard care	1	469	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.75, 1.07]
3 Any breastfeeding at 6 months	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 BF education workshop versus standard care	1	178	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.87, 1.51]
3.2 BF practical skills versus standard care	1	596	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.87, 1.17]
3.3 BF attitude education versus standard care	1	592	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.79, 1.07]
3.4 BF education session versus standard care	2	569	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.86, 1.19]
4 Exclusive breastfeeding at 3 months	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 BF education workshop versus standard care	1	185	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.84, 1.38]
4.2 BF education session versus standard care	2	637	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.85, 1.30]
5 Exclusive breastfeeding at 6 months	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 BF education workshop versus standard care	1	178	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.70, 1.80]
5.2 BF practical skills versus standard care	1	596	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.69, 2.05]
5.3 Formal BF attitude versus standard care	1	592	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.67, 2.01]
5.4 BF education session versus standard care	2	1094	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.80, 1.31]
6 Initiation of breastfeeding	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 BF education workshop versus standard care	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.97, 1.45]
6.2 Peer counselling versus standard care	1	59	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [1.13, 2.93]
6.3 BF practical skills versus standard care	1	616	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.98, 1.04]

6.4 BF attitude education versus standard care	1	618	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.95, 1.02]
6.5 BF education session versus standard care	2	1327	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.98, 1.09]
6.6 BF education video versus standard care	1	346	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.80, 1.23]
6.7 LC versus standard care	1	144	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.86, 2.07]
7 Initiation of BF (cluster-randomised trial)	2		Odds Ratio (Fixed, 95% CI)	Subtotals only
7.1 Peer counselling versus standard care	1	2398	Odds Ratio (Fixed, 95% CI)	1.11 [0.86, 1.43]
7.2 Group LC session versus standard care	1	1249	Odds Ratio (Fixed, 95% CI)	1.20 [0.80, 1.80]
8 Mastitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 LC versus standard care	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 4.02]
9 Breastfeeding complication (nipple pain)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 LC versus standard care	1	70	Mean Difference (IV, Fixed, 95% CI)	-19.8 [-23.23, -16.37]
10 Breastfeeding complication (nipple trauma)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.1 LC versus standard care	1	70	Mean Difference (IV, Fixed, 95% CI)	38.65 [32.95, 44.35]
11 Breastfeeding problems	1	1162	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.70, 1.43]
11.1 BF education session versus standard care	1	1162	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.70, 1.43]

Comparison 2. One type of BF education versus a different type of BF education

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any breastfeeding at 3 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Group education versus individual education	1	74	Risk Ratio (M-H, Fixed, 95% CI)	2.84 [0.61, 13.18]
2 Any breastfeeding at 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 BF practical skills versus BF attitude education	1	590	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.94, 1.28]
3 Exclusive breastfeeding at 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 BF practical skills versus BF attitude education	1	590	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.61, 1.73]
4 Initiation of BF	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 BF practical skills versus BF attitude education	1	614	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.99, 1.06]

Comparison 3. Multiple methods of BF education versus a single method of BF education

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of any breastfeeding (days)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 BF education session plus commitment to exclusive BF versus BF education session	1	18	Mean Difference (IV, Fixed, 95% CI)	8.0 [-6.84, 22.84]
2 Any breastfeeding at 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Video + education session versus pamphlets	1	175	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [0.86, 2.94]

Comparison 4. Different combinations of multiple methods of providing BF education

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any breastfeeding at 4 months (cluster-randomised trial)	1		Odds Ratio (Fixed, 95% CI)	Subtotals only
1.1 LC + BF booklet + 24 h free LC versus BF booklet + phone number for BF questions and problems.	1	698	Odds Ratio (Fixed, 95% CI)	0.82 [0.58, 1.16]
2 Exclusive breastfeeding at 3 months	2		Odds Ratio (Fixed, 95% CI)	Subtotals only
2.1 LC + BF booklet + 24 hrs free LC versus BF booklet + phone number for BF questions and problems.	1	698	Odds Ratio (Fixed, 95% CI)	0.79 [0.57, 1.09]
2.2 BF booklet + video + LC versus BF booklet + video	1	150	Odds Ratio (Fixed, 95% CI)	1.40 [0.70, 2.80]
3 Exclusive breastfeeding at 6 months	1		Odds Ratio (Fixed, 95% CI)	Subtotals only
3.1 BF booklet + video + LC versus BF booklet + video	1	169	Odds Ratio (Fixed, 95% CI)	2.50 [1.00, 6.25]

Comparison 5. Multiple methods of BF education versus standard/routine care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of any breastfeeding (days)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 BF education session plus commitment to exclusive BF versus standard care	1	16	Mean Difference (IV, Fixed, 95% CI)	14.20 [-2.97, 31.37]
2 Exclusive breastfeeding at 3 months	2		Odds Ratio (Fixed, 95% CI)	Subtotals only
2.1 BF booklet + video + LC versus standard care	1	159	Odds Ratio (Fixed, 95% CI)	2.60 [1.25, 5.40]
2.2 BF booklet + video versus standard care	1	159	Odds Ratio (Fixed, 95% CI)	1.80 [0.80, 4.05]
2.3 Monthly BF session + weekly cell phone message versus standard care	1	390	Odds Ratio (Fixed, 95% CI)	1.80 [1.10, 2.95]
3 Exclusive breastfeeding at six months	2		Odds Ratio (Fixed, 95% CI)	Subtotals only
3.1 BF booklet + video + LC versus standard care	1	175	Odds Ratio (Fixed, 95% CI)	2.40 [1.00, 5.76]
3.2 BF booklet + video versus standard care	1	184	Odds Ratio (Fixed, 95% CI)	0.90 [0.30, 2.70]
3.3 Monthly BF session + weekly cell phone message versus standard care	1	390	Odds Ratio (Fixed, 95% CI)	2.40 [1.40, 4.11]
4 Initiation of breastfeeding	1		Odds Ratio (Fixed, 95% CI)	Subtotals only
4.1 Monthly BF session + weekly cell phone message versus standard care	1	380	Odds Ratio (Fixed, 95% CI)	2.61 [1.61, 4.24]

Comparison 6. Summary of findings: one type of BF education versus standard/routine care

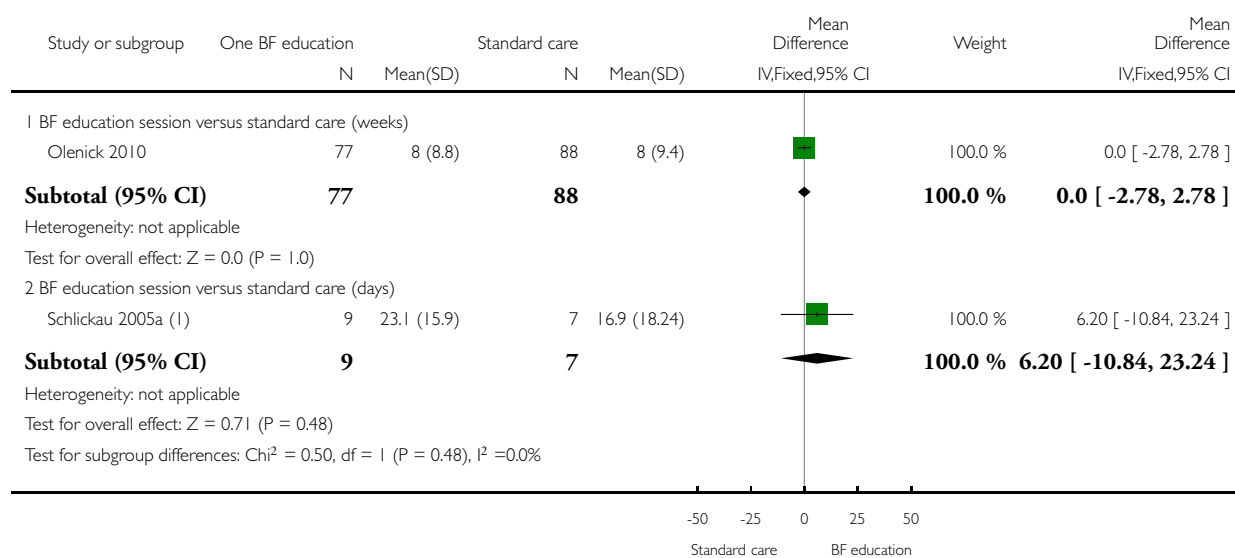
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Initiation of breastfeeding	8	3505	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.94, 1.09]
2 Exclusive breastfeeding at 3 months	3	822	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.90, 1.25]
3 Exclusive breastfeeding at 6 months	4	2161	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.87, 1.30]
4 Any breastfeeding at 3 months	2	654	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.82, 1.18]
5 Any breastfeeding at 6 months	4	1636	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.90, 1.23]

Analysis 1.1. Comparison 1 One type of BF education versus standard/routine care, Outcome 1 Duration of any breastfeeding.

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 1 One type of BF education versus standard/routine care

Outcome: 1 Duration of any breastfeeding



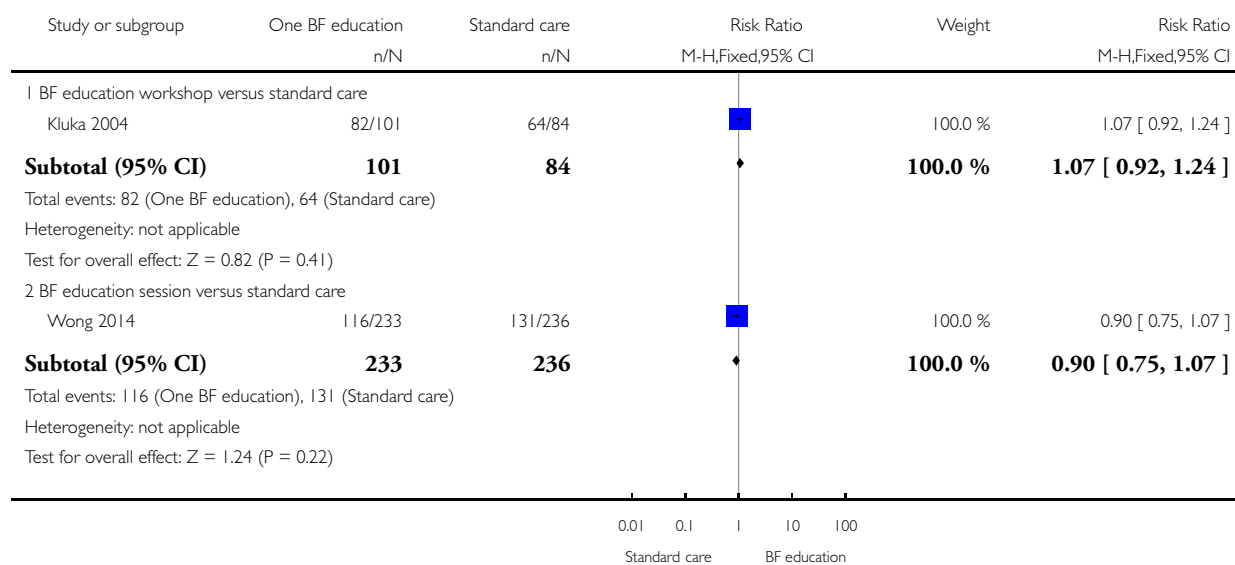
(1) First level PBE versus control

Analysis 1.2. Comparison 1 One type of BF education versus standard/routine care, Outcome 2 Any breastfeeding at 3 months.

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 1 One type of BF education versus standard/routine care

Outcome: 2 Any breastfeeding at 3 months

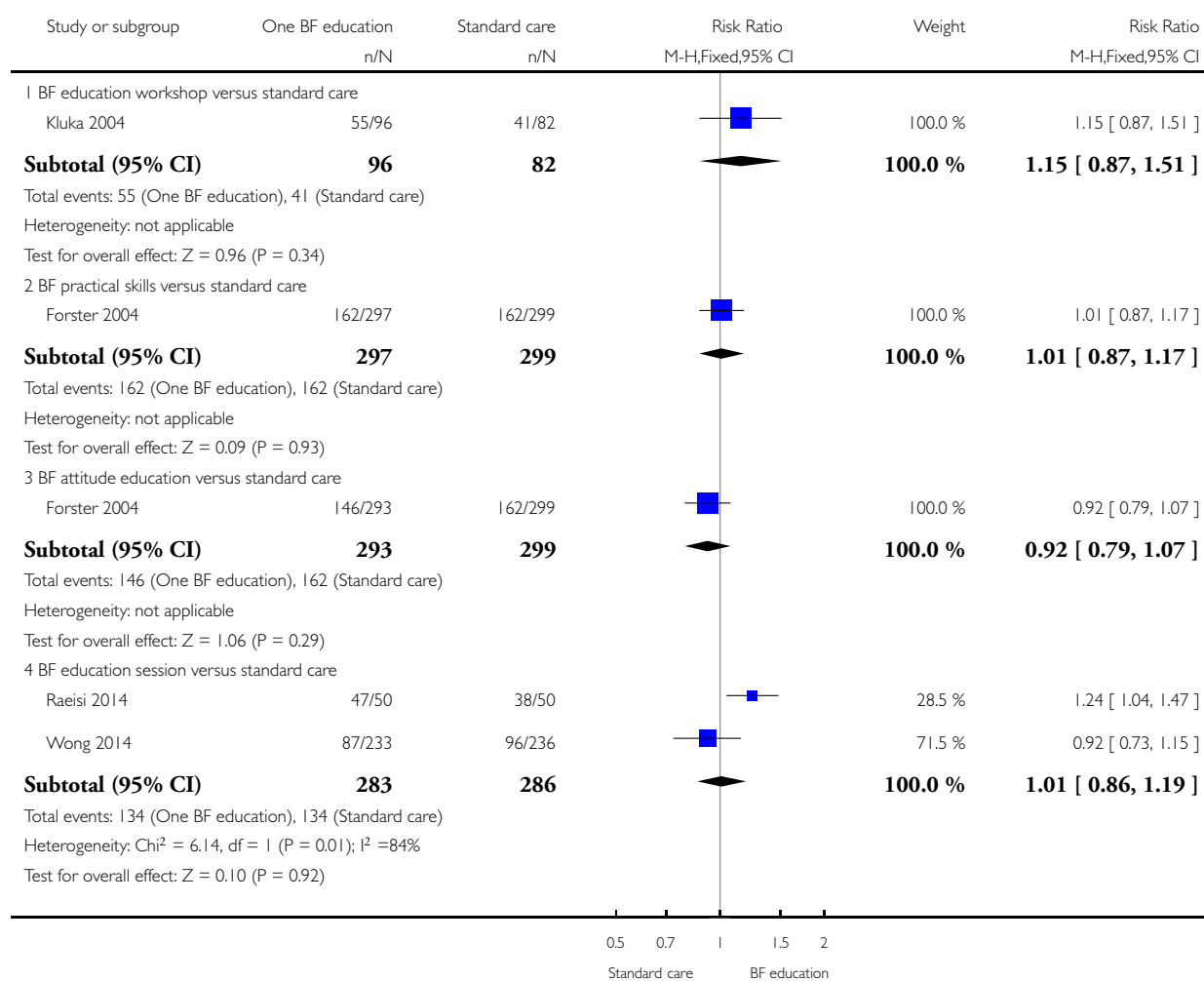


Analysis 1.3. Comparison 1 One type of BF education versus standard/routine care, Outcome 3 Any breastfeeding at 6 months.

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 1 One type of BF education versus standard/routine care

Outcome: 3 Any breastfeeding at 6 months

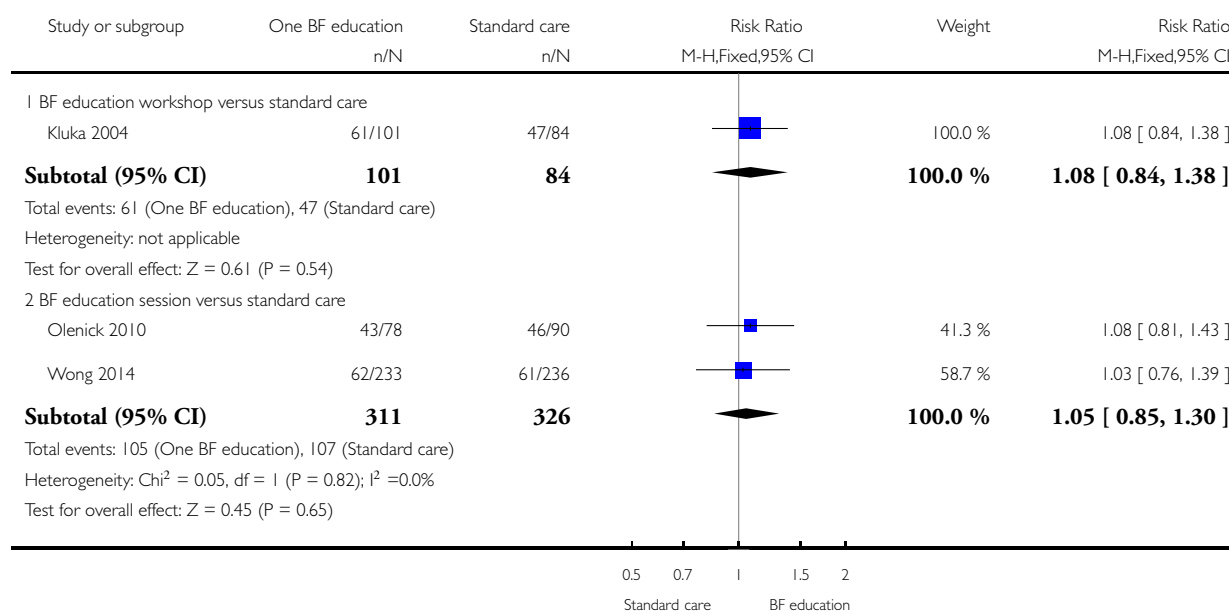


Analysis 1.4. Comparison 1 One type of BF education versus standard/routine care, Outcome 4 Exclusive breastfeeding at 3 months.

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 1 One type of BF education versus standard/routine care

Outcome: 4 Exclusive breastfeeding at 3 months

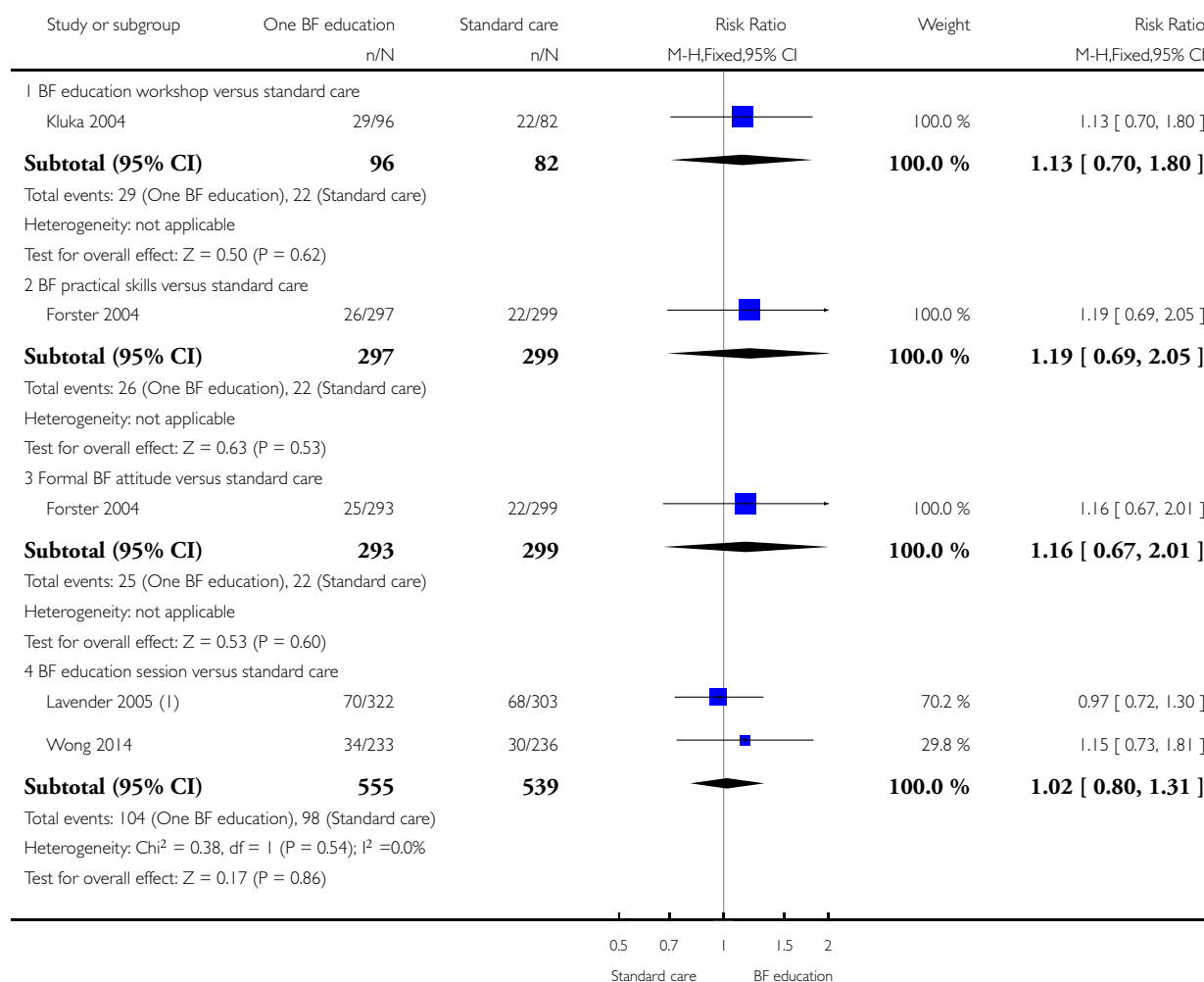


Analysis 1.5. Comparison 1 One type of BF education versus standard/routine care, Outcome 5 Exclusive breastfeeding at 6 months.

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 1 One type of BF education versus standard/routine care

Outcome: 5 Exclusive breastfeeding at 6 months



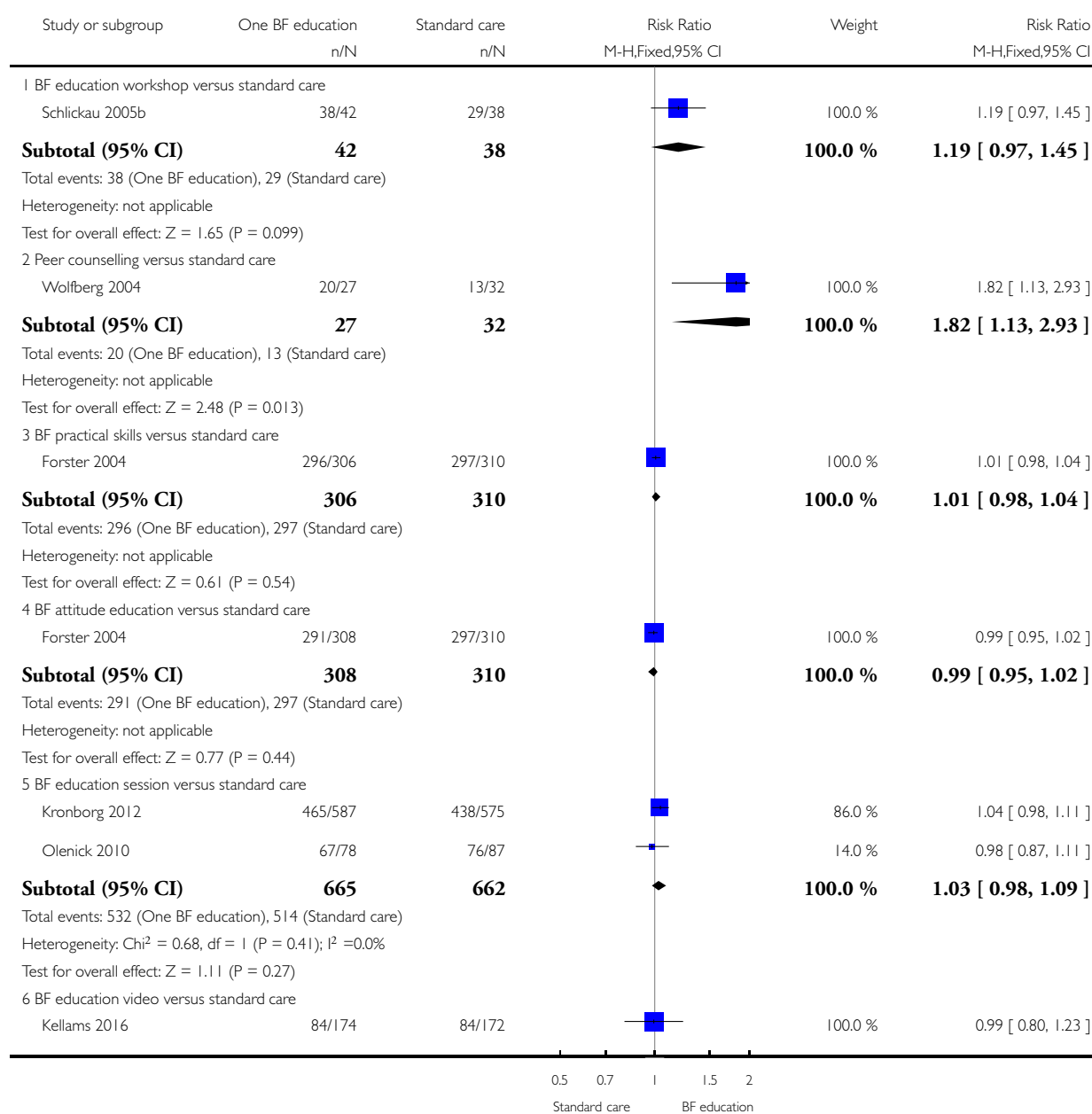
(1) Cluster-adjusted using a design effect of 2. Raw data 140/644 education and 138/605 standard care.

Analysis 1.6. Comparison 1 One type of BF education versus standard/routine care, Outcome 6 Initiation of breastfeeding.

Review: Antenatal breastfeeding education for increasing breastfeeding duration

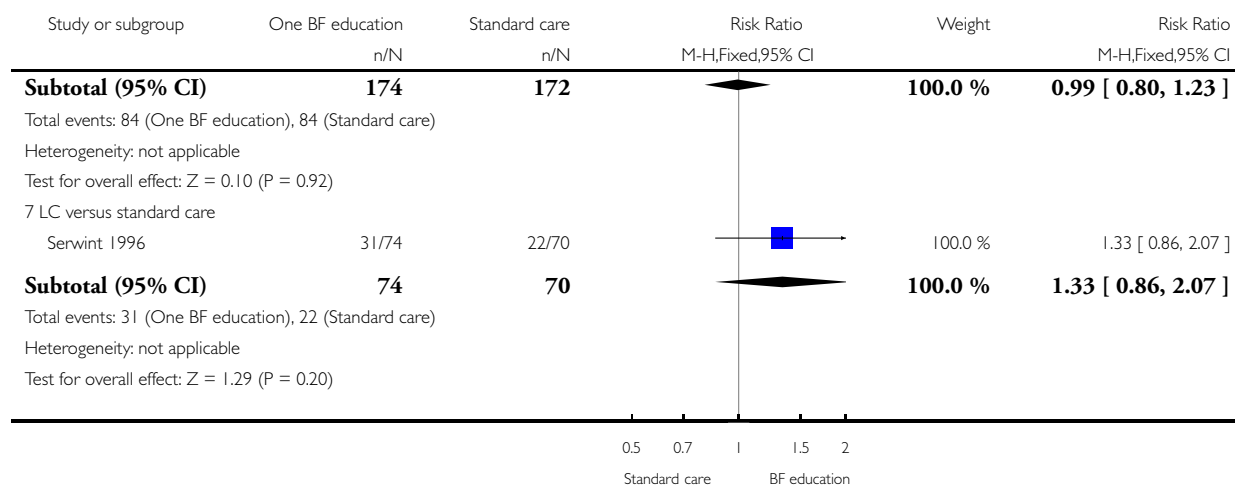
Comparison: 1 One type of BF education versus standard/routine care

Outcome: 6 Initiation of breastfeeding



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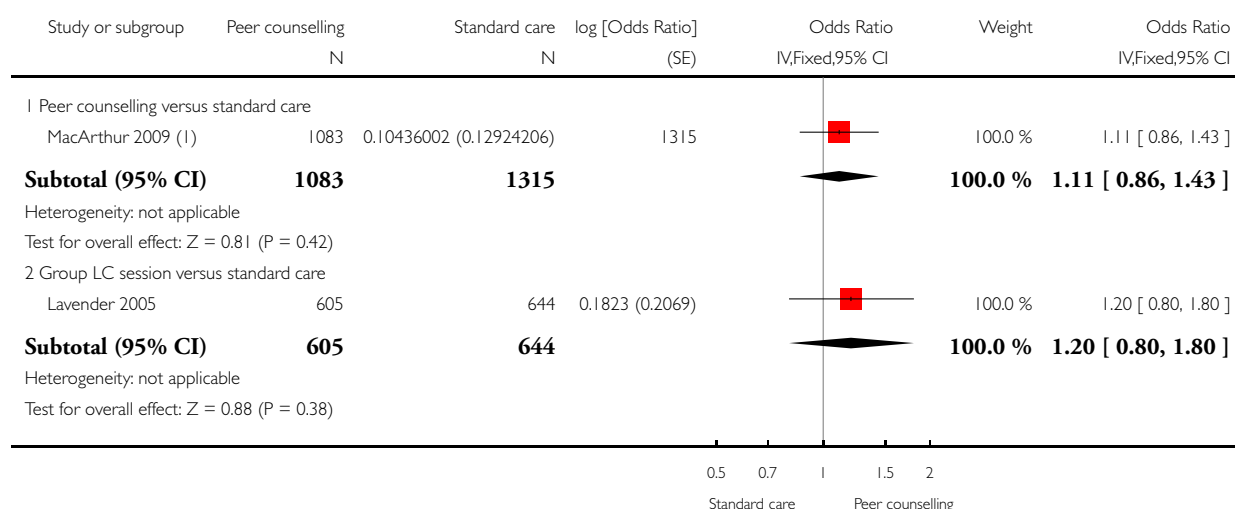


Analysis 1.7. Comparison 1 One type of BF education versus standard/routine care, Outcome 7 Initiation of BF (cluster-randomised trial).

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 1 One type of BF education versus standard/routine care

Outcome: 7 Initiation of BF (cluster-randomised trial)



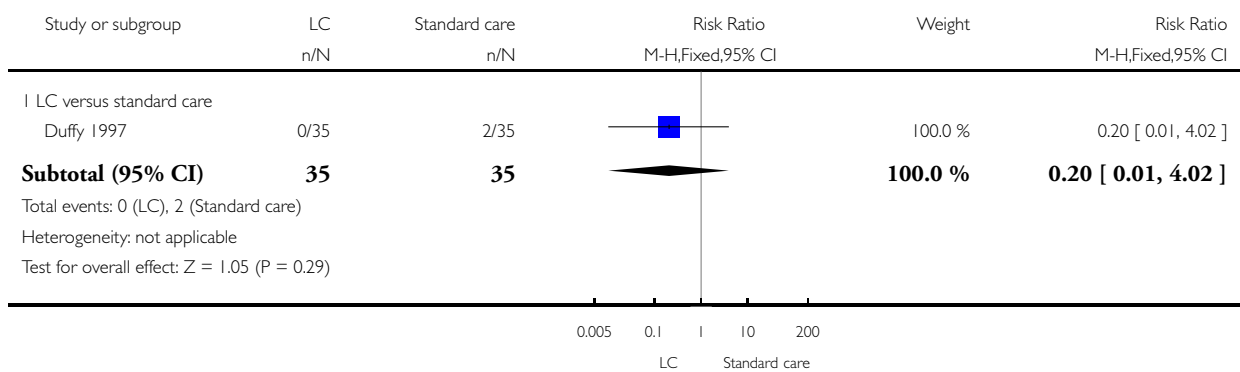
(I) Adjusted for clustering.

Analysis 1.8. Comparison 1 One type of BF education versus standard/routine care, Outcome 8 Mastitis.

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 1 One type of BF education versus standard/routine care

Outcome: 8 Mastitis

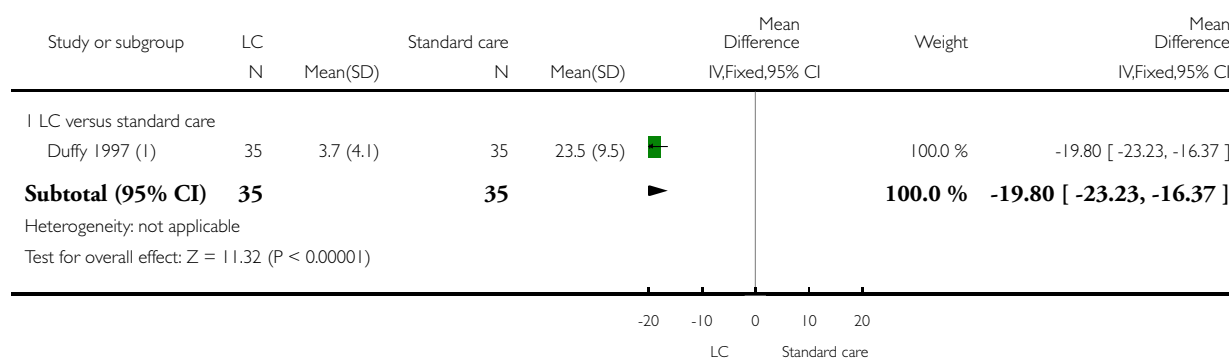


Analysis 1.9. Comparison 1 One type of BF education versus standard/routine care, Outcome 9 Breastfeeding complication (nipple pain).

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 1 One type of BF education versus standard/routine care

Outcome: 9 Breastfeeding complication (nipple pain)



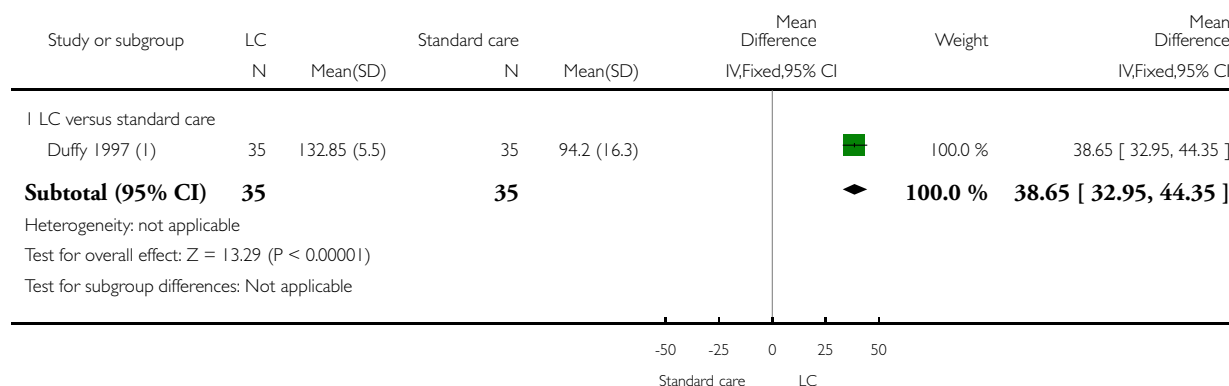
(1) VAS score 0-10 with 10 greatest pain possible, scored daily for four days and added together (possible 0-40).

Analysis 1.10. Comparison 1 One type of BF education versus standard/routine care, Outcome 10 Breastfeeding complication (nipple trauma).

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 1 One type of BF education versus standard/routine care

Outcome: 10 Breastfeeding complication (nipple trauma)



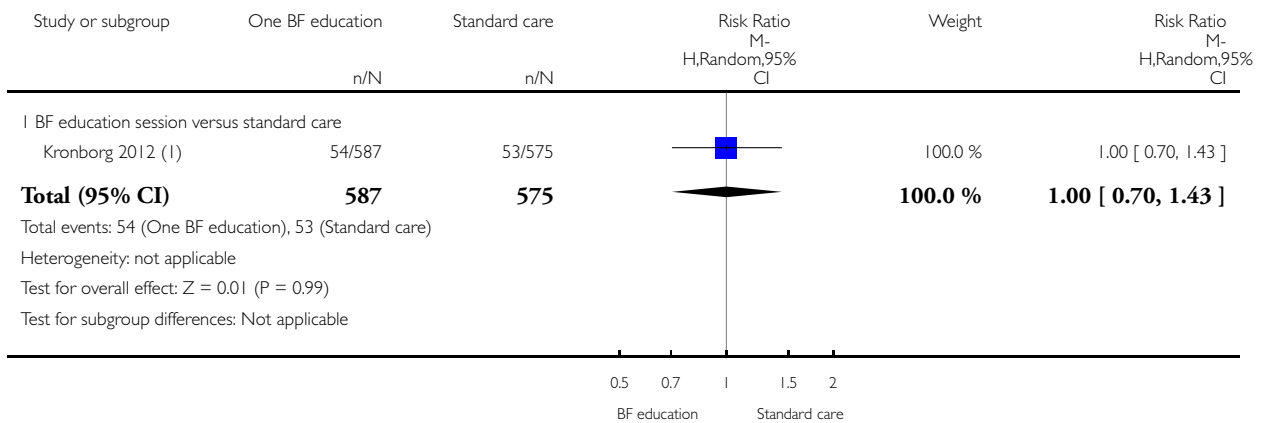
(I) A higher score indicates less nipple trauma. Possible daily range 0-36. The score is a composite of the first 4 days post birth.

Analysis 1.11. Comparison 1 One type of BF education versus standard/routine care, Outcome 11 Breastfeeding problems.

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 1 One type of BF education versus standard/routine care

Outcome: 11 Breastfeeding problems



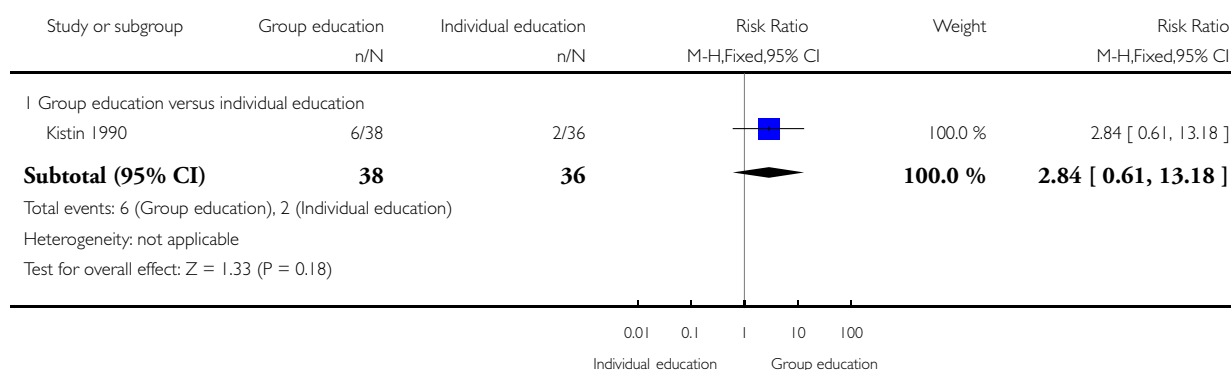
(1) BF problems as measured with the following yes no question: If it has been difficult or very difficult what was the reason. Has it been breastfeeding problems?

Analysis 2.1. Comparison 2 One type of BF education versus a different type of BF education, Outcome 1 Any breastfeeding at 3 months.

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 2 One type of BF education versus a different type of BF education

Outcome: 1 Any breastfeeding at 3 months

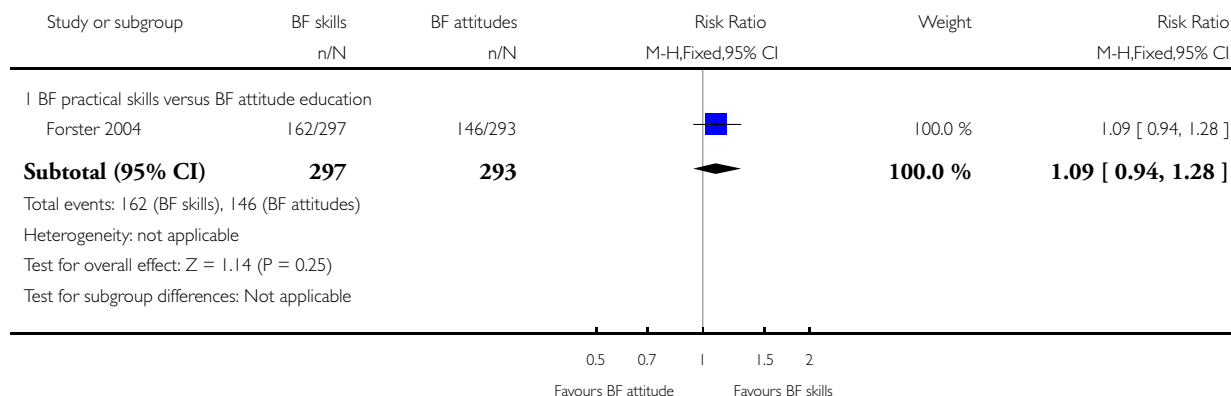


Analysis 2.2. Comparison 2 One type of BF education versus a different type of BF education, Outcome 2 Any breastfeeding at 6 months.

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 2 One type of BF education versus a different type of BF education

Outcome: 2 Any breastfeeding at 6 months

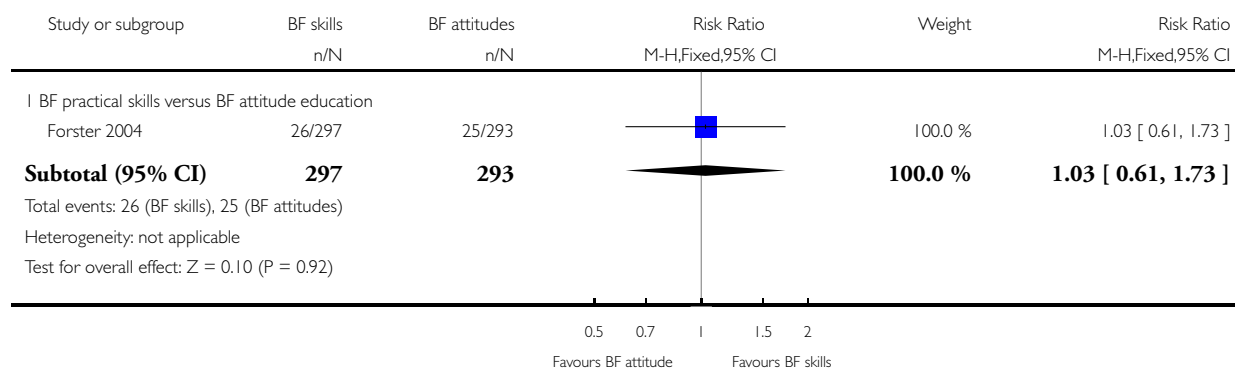


Analysis 2.3. Comparison 2 One type of BF education versus a different type of BF education, Outcome 3 Exclusive breastfeeding at 6 months.

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 2 One type of BF education versus a different type of BF education

Outcome: 3 Exclusive breastfeeding at 6 months

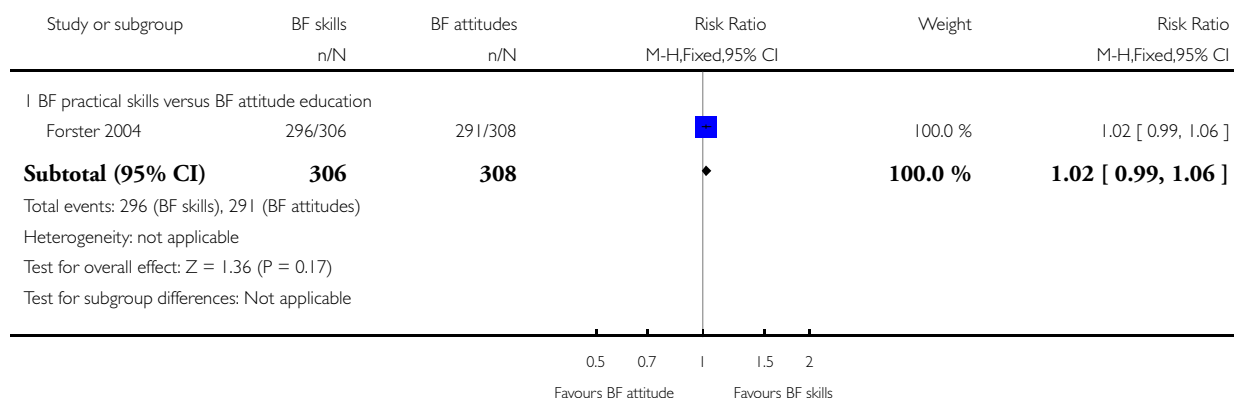


Analysis 2.4. Comparison 2 One type of BF education versus a different type of BF education, Outcome 4 Initiation of BF.

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 2 One type of BF education versus a different type of BF education

Outcome: 4 Initiation of BF

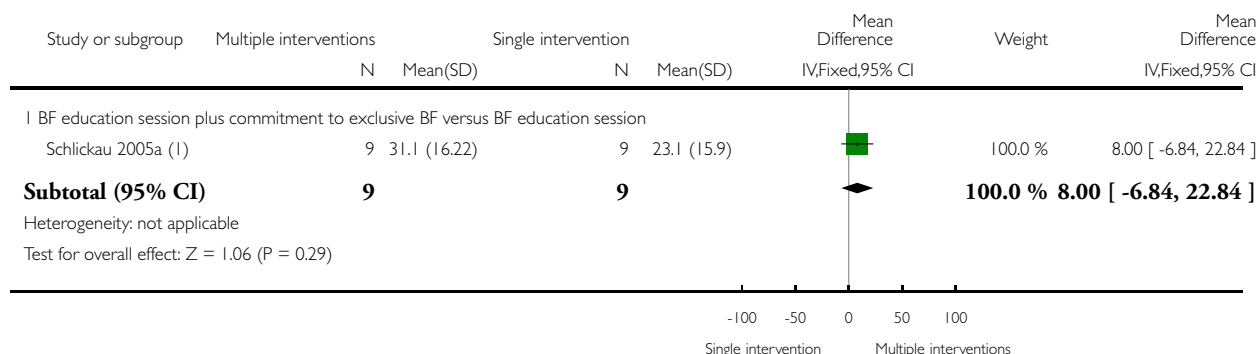


Analysis 3.1. Comparison 3 Multiple methods of BF education versus a single method of BF education, Outcome 1 Duration of any breastfeeding (days).

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 3 Multiple methods of BF education versus a single method of BF education

Outcome: 1 Duration of any breastfeeding (days)



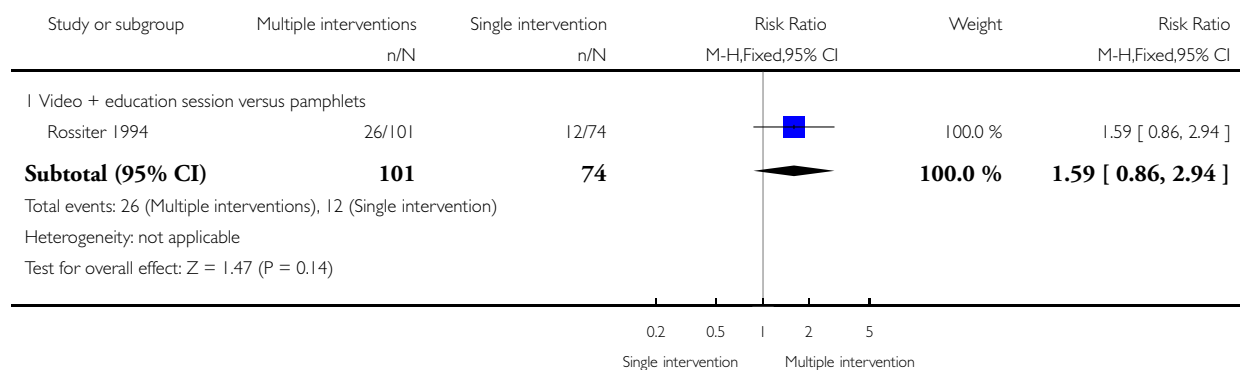
(1) Two level intervention versus control

Analysis 3.2. Comparison 3 Multiple methods of BF education versus a single method of BF education, Outcome 2 Any breastfeeding at 6 months.

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 3 Multiple methods of BF education versus a single method of BF education

Outcome: 2 Any breastfeeding at 6 months

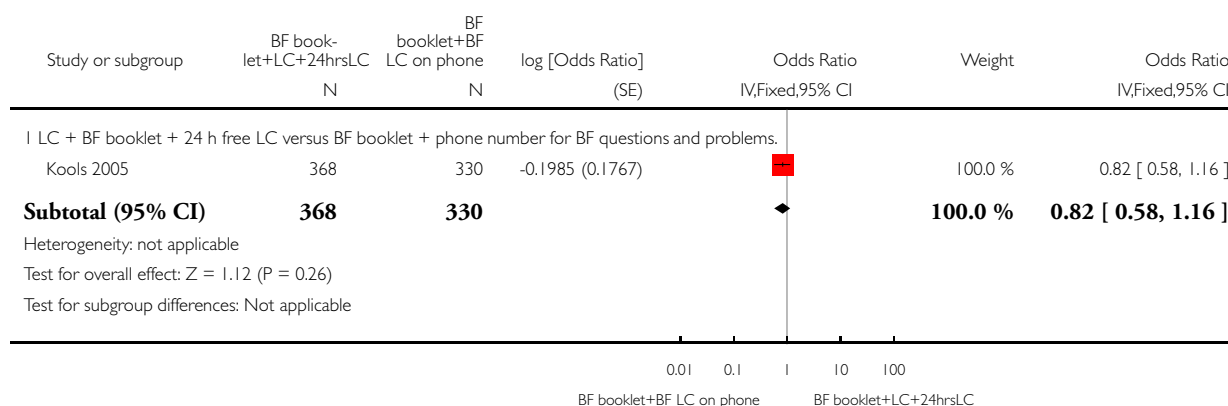


Analysis 4.1. Comparison 4 Different combinations of multiple methods of providing BF education, Outcome 1 Any breastfeeding at 4 months (cluster-randomised trial).

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 4 Different combinations of multiple methods of providing BF education

Outcome: 1 Any breastfeeding at 4 months (cluster-randomised trial)

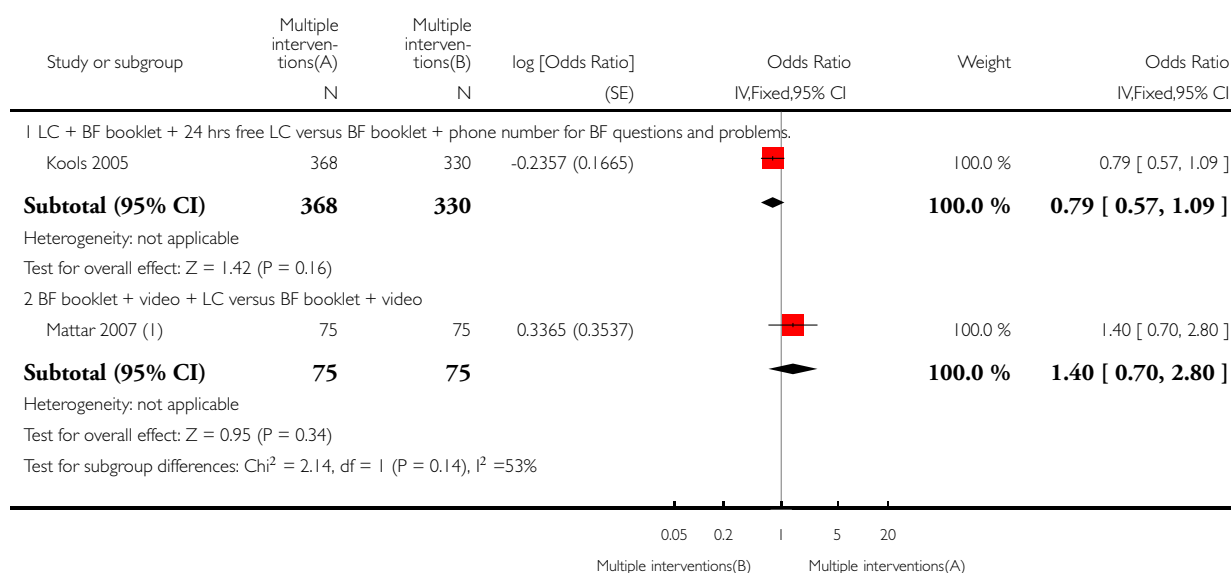


Analysis 4.2. Comparison 4 Different combinations of multiple methods of providing BF education, Outcome 2 Exclusive breastfeeding at 3 months.

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 4 Different combinations of multiple methods of providing BF education

Outcome: 2 Exclusive breastfeeding at 3 months



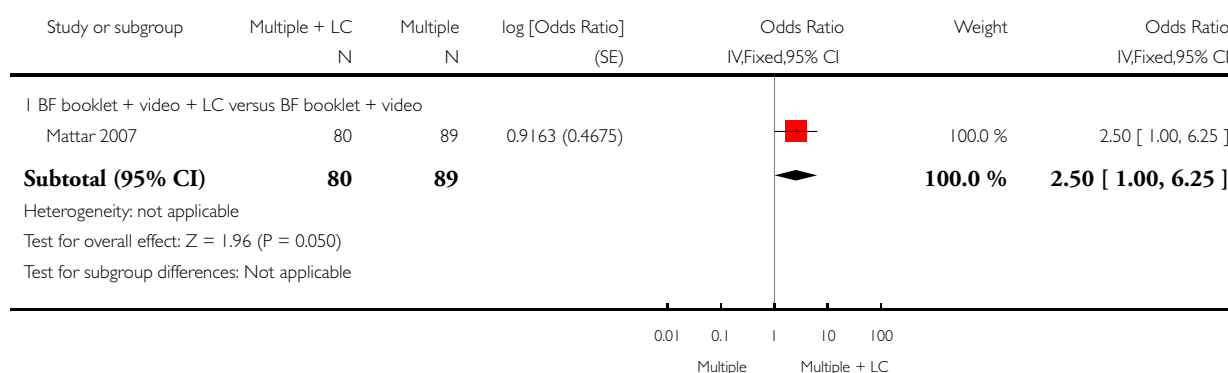
(1) Compares intervention arms A and B.

Analysis 4.3. Comparison 4 Different combinations of multiple methods of providing BF education, Outcome 3 Exclusive breastfeeding at 6 months.

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 4 Different combinations of multiple methods of providing BF education

Outcome: 3 Exclusive breastfeeding at 6 months

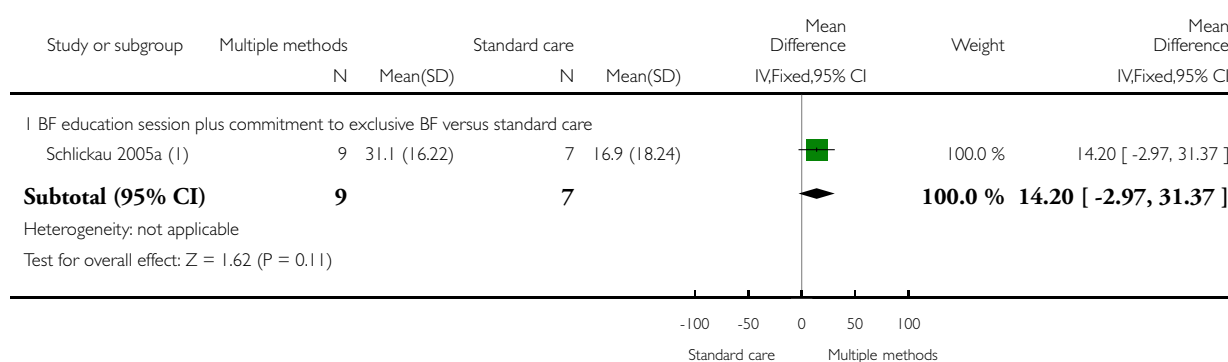


Analysis 5.1. Comparison 5 Multiple methods of BF education versus standard/routine care, Outcome 1 Duration of any breastfeeding (days).

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 5 Multiple methods of BF education versus standard/routine care

Outcome: 1 Duration of any breastfeeding (days)



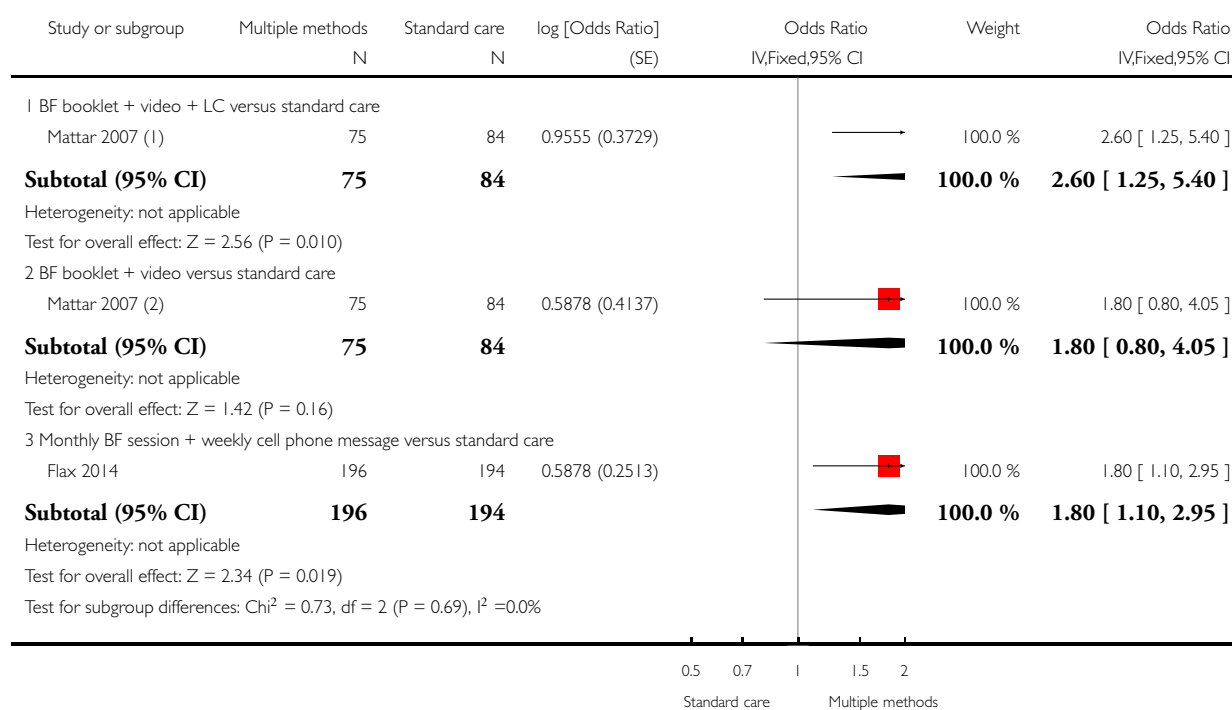
(1) Two level intervention versus control

Analysis 5.2. Comparison 5 Multiple methods of BF education versus standard/routine care, Outcome 2 Exclusive breastfeeding at 3 months.

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 5 Multiple methods of BF education versus standard/routine care

Outcome: 2 Exclusive breastfeeding at 3 months



(1) Compares arms A and C

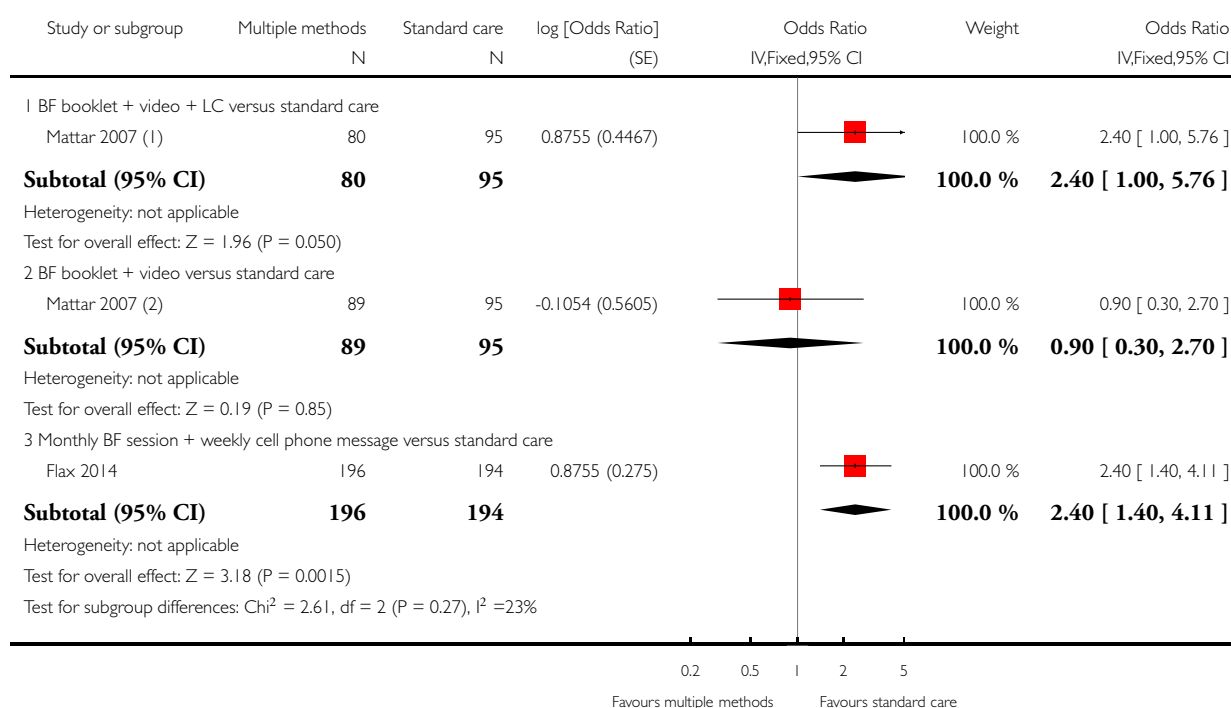
(2) Compares arms B and C

Analysis 5.3. Comparison 5 Multiple methods of BF education versus standard/routine care, Outcome 3 Exclusive breastfeeding at six months.

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 5 Multiple methods of BF education versus standard/routine care

Outcome: 3 Exclusive breastfeeding at six months



(1) Compares arms A and C

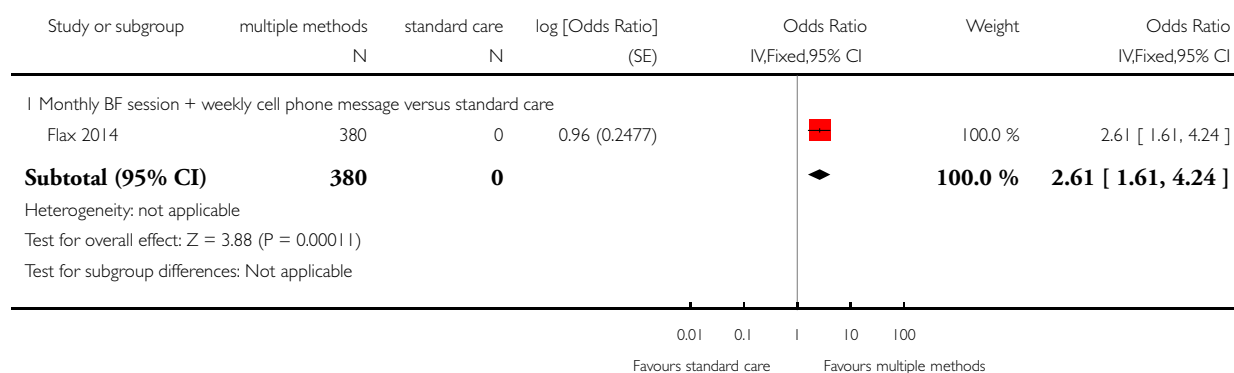
(2) Compares arms B and C

Analysis 5.4. Comparison 5 Multiple methods of BF education versus standard/routine care, Outcome 4 Initiation of breastfeeding.

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 5 Multiple methods of BF education versus standard/routine care

Outcome: 4 Initiation of breastfeeding

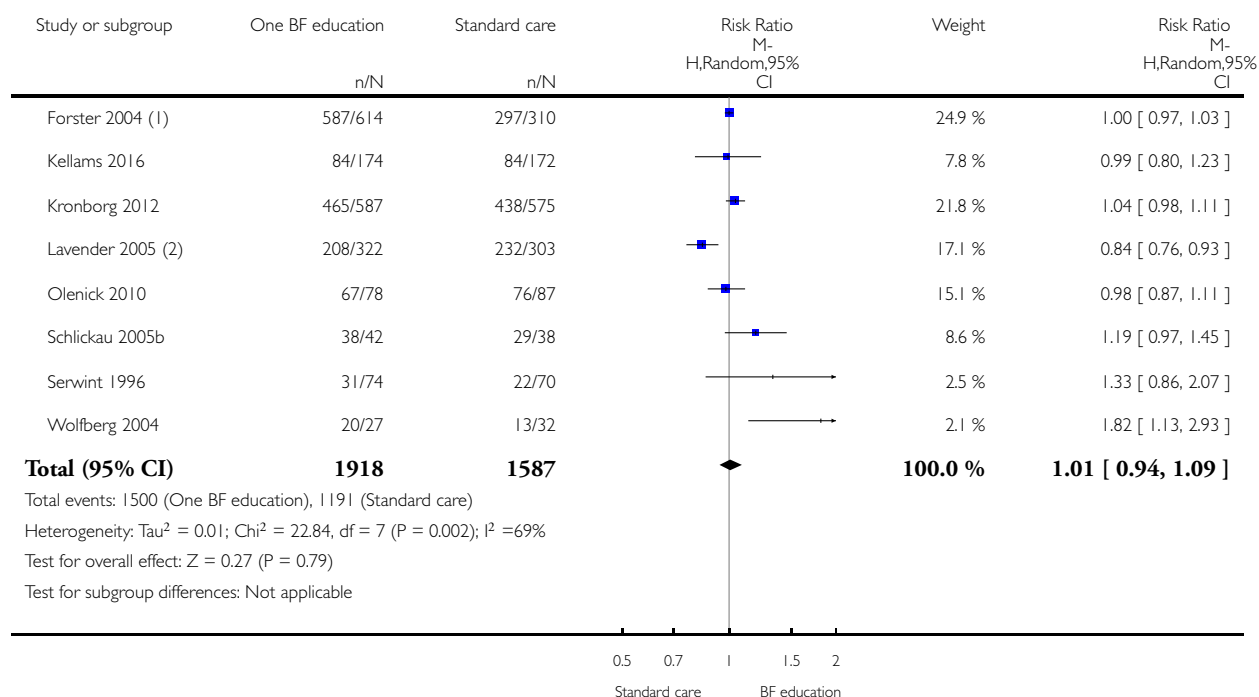


Analysis 6.1. Comparison 6 Summary of findings: one type of BF education versus standard/routine care, Outcome 1 Initiation of breastfeeding.

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 6 Summary of findings: one type of BF education versus standard/routine care

Outcome: 1 Initiation of breastfeeding



(1) Groups with practical skills + group with attitude versus standard care

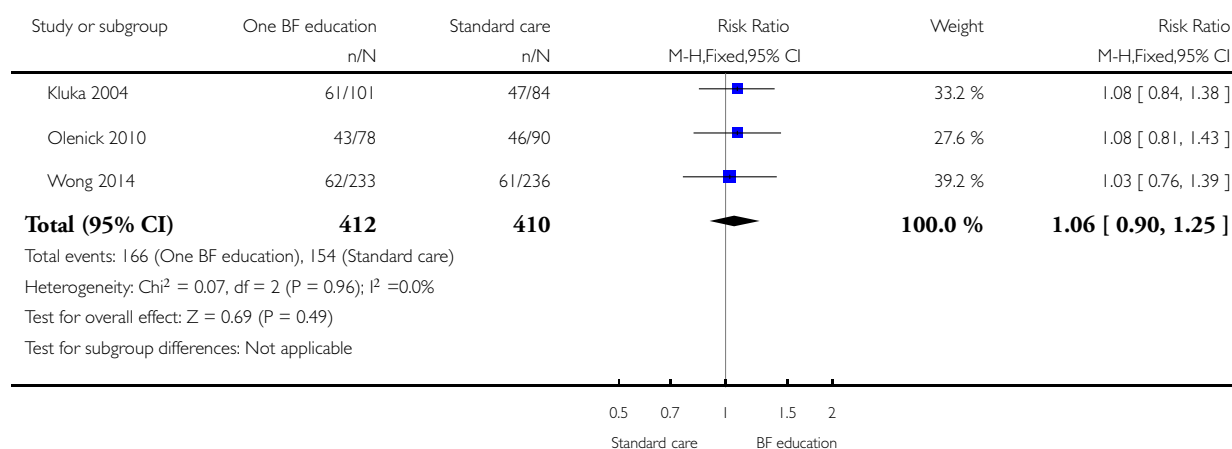
(2) Breastfeeding at discharge: adjusted with design effect of 2. Original data 463/605 standard care and 517/644 education.

Analysis 6.2. Comparison 6 Summary of findings: one type of BF education versus standard/routine care, Outcome 2 Exclusive breastfeeding at 3 months.

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 6 Summary of findings: one type of BF education versus standard/routine care

Outcome: 2 Exclusive breastfeeding at 3 months

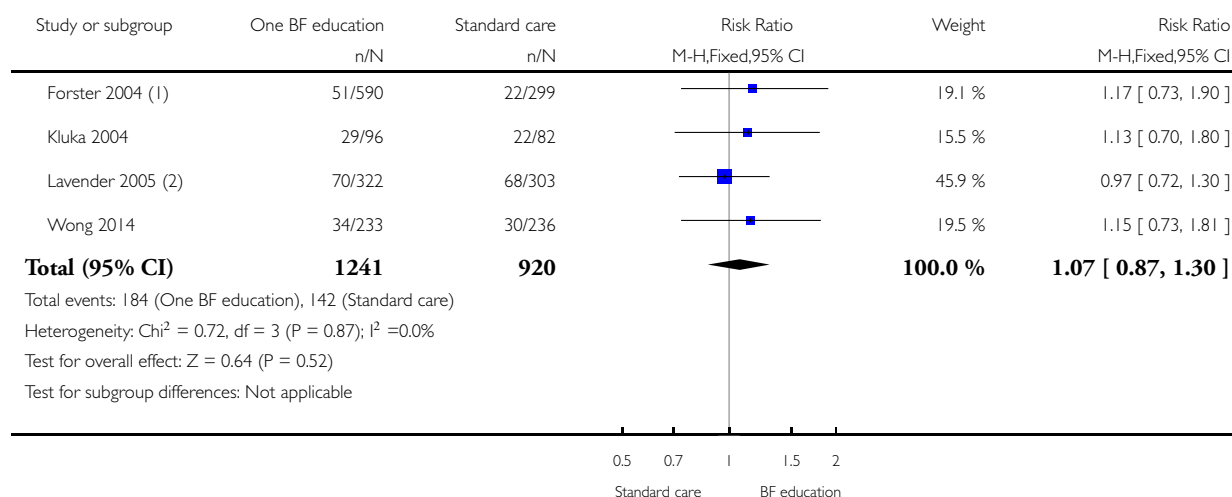


Analysis 6.3. Comparison 6 Summary of findings: one type of BF education versus standard/routine care, Outcome 3 Exclusive breastfeeding at 6 months.

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 6 Summary of findings: one type of BF education versus standard/routine care

Outcome: 3 Exclusive breastfeeding at 6 months



(1) Skills + Attitudes arms versus standard care

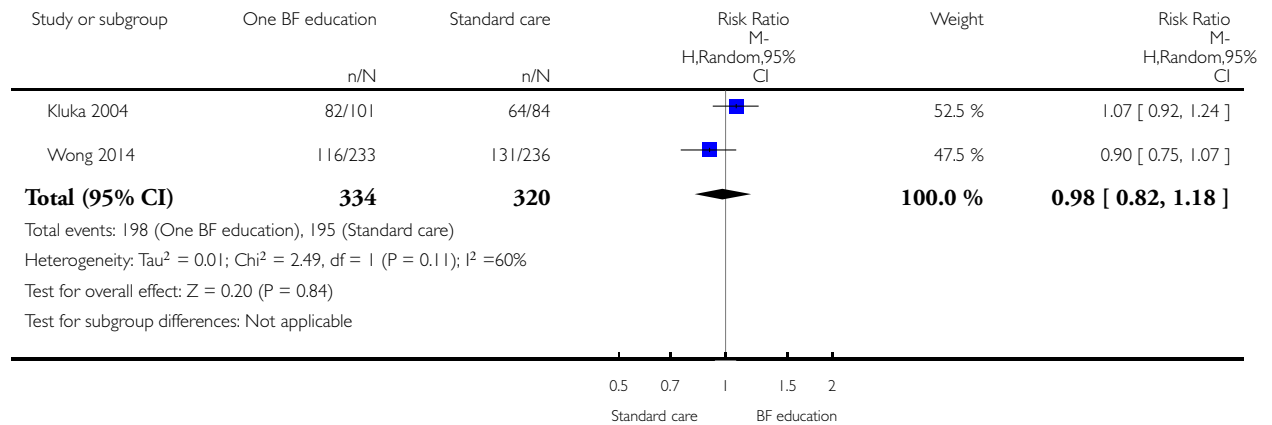
(2) Cluster-adjusted using a design effect of 2. Raw data 140/644 education and 138/605 standard care.

Analysis 6.4. Comparison 6 Summary of findings: one type of BF education versus standard/routine care, Outcome 4 Any breastfeeding at 3 months.

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 6 Summary of findings: one type of BF education versus standard/routine care

Outcome: 4 Any breastfeeding at 3 months

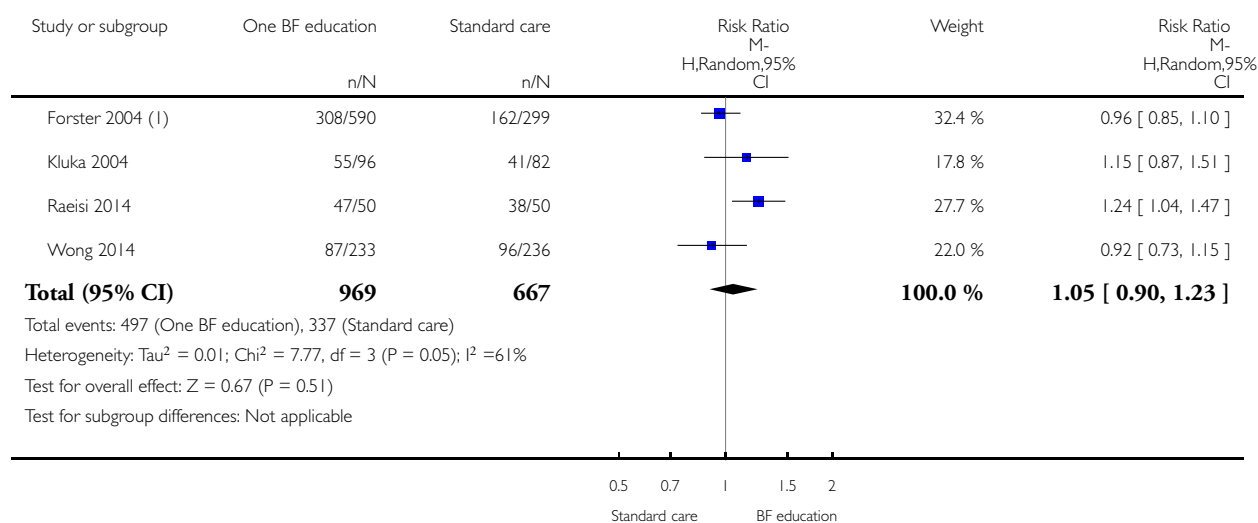


Analysis 6.5. Comparison 6 Summary of findings: one type of BF education versus standard/routine care, Outcome 5 Any breastfeeding at 6 months.

Review: Antenatal breastfeeding education for increasing breastfeeding duration

Comparison: 6 Summary of findings: one type of BF education versus standard/routine care

Outcome: 5 Any breastfeeding at 6 months



(1) Skills + Attitudes arms versus standard care.

APPENDICES

Appendix I. Search strategies

Authors wrote and ran these searches.

CENTRAL (*The Cochrane Library 2016, Issue 3*)

#1 antenatal (MeSH)

#2 prenatal (MeSH)

#3 education*

#4 BF

#5 (breast next feeding)

#6 breastfeeding

#7 lactation*

#8 nursing

#9 (#1 or #2)

#10 (#4 or #5 or #6 or #7 or #8)

#11 (#9 and #3 and #10)

MEDLINE (January 1966 to 1 March 2016) and **SCOPUS** (January 1985 to 1 March 2016)

#1 antenatal[tiab]

#2 prenatal care[mh]
 #3 (#1 or #2)
 #4 breastfeeding
 #5 breast feeding
 #6 lactation
 #7 nursing
 #8(#4 or #5 or #6 or #7)
 #9 randomised controlled trial[pt]
 #10 controlled clinical trial[pt]
 #11 randomised[tiab]
 #12 placebo[tiab]
 #13 groups[tiab]
 #14 cluster[tiab]
 #15(#9 or #10 or #11 or #12 or #13 or #14)
 #16 education
 #17 (#3 and #8 and #15 and #16)

WHAT'S NEW

Last assessed as up-to-date: 1 March 2016.

Date	Event	Description
1 March 2016	New citation required but conclusions have not changed	Five new trials incorporated, 'Summary of findings' table added, analyses re-structured to provide meaningful data for 'Summary of findings' table
1 March 2016	New search has been performed	Search updated and five new trials added (Flax 2014 ; Kellams 2016 ; Pate 2009 ; Raeisi 2014 ; Wong 2014).

HISTORY

Protocol first published: Issue 2, 2007

Review first published: Issue 11, 2011

Date	Event	Description
2 June 2012	New citation required but conclusions have not changed	Review updated.
2 June 2012	New search has been performed	Search updated in November 2011. Two new studies included (Kronborg 2011 ; Olenick 2010) and three excluded (Kupratakul 2010 ; NCT01383070 ; Wockel 2009).
7 October 2011	Amended	Sources of support edited.

(Continued)

17 April 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

P Lumbiganon (PL) and M Laopaiboon (ML) screened Titles and Abstracts to select potential studies. Ruth Martis (RM), Jacqueline Ho (JH) Mario Festin (MF), ML and PL selected potential studies to include or exclude. ML and PL revised data analysis, drafted the update review. All review authors approved the final version of the review.

DECLARATIONS OF INTEREST

Pisake Lumbiganon: none known

Ruth Martis: A bursary from the Cochrane Health Promotion and Public Health Field was provided to support Ruth Martis to travel to a review authors meeting in Australia. The bursary was administrated by the SEA-ORCHID project.

Malinee Laopaiboon: none known

Mario R Festin: I was employed as Medical officer and as fixed term staff from 2007 to early 2008 at the WHO and as professional staff (Lead Specialist) at the WHO HQ in Geneva from early 2009 to present. I received payment from United Laboratories Philippines from 2006 to 2007 on use of antibiotics in gynecologic surgery.

Jacqueline J Ho: none known

Mohammad Hakimi: none known

SOURCES OF SUPPORT

Internal sources

- Khon Kaen University, Thailand.
- The University of Adelaide, Australia.
- University of Philippines, Philippines.
- Gadjah Mada University, Indonesia.
- Royal College of Medicine Perak, Malaysia.
- Penang Medical College, Malaysia.

External sources

- Thailand Research Fund (Outstanding Professor Award), Thailand.
- Wellcome Trust, UK.
- Cochrane Health Promotion and Public Health (HPPH) Field, Australia.
- Evidence and Programme Guidance Unit, Department of Nutrition for Health and Development, World Health Organization, Switzerland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added one more comparison of 'programmes involving multiple methods of providing education versus no formal education' to our subgroup analysis. We searched SCOPUS instead of Embase because our university subscribed to SCOPUS but not Embase.

Non-prespecified outcomes

Two studies reported BF practices at time points not pre-specified for this review. One study ([Noel-Weiss 2006](#)) reported any BF at eight weeks and exclusive BF at eight weeks. Another study reported BF outcomes at seven days ([Ryser 2004](#)).

A 'Summary of findings' table has been incorporated in this update (2016).

INDEX TERMS

Medical Subject Headings (MeSH)

*Breast Feeding [statistics & numerical data]; Counseling [methods]; Mothers [*education]; Peer Group; Prenatal Care [*methods]; Randomized Controlled Trials as Topic; Time Factors

MeSH check words

Female; Humans; Pregnancy



Cochrane
Library

Cochrane Database of Systematic Reviews

Behavioural interventions to promote workers' use of respiratory protective equipment (Review)

Luong Thanh BY, Laopaiboon M, Koh D, Sakunkoo P, Moe H

Luong Thanh BY, Laopaiboon M, Koh D, Sakunkoo P, Moe H.

Behavioural interventions to promote workers' use of respiratory protective equipment.

Cochrane Database of Systematic Reviews 2016, Issue 12. Art. No.: CD010157.

DOI: 10.1002/14651858.CD010157.pub2.

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	4
BACKGROUND	5
OBJECTIVES	6
METHODS	6
RESULTS	9
Figure 1.	10
Figure 2.	14
Figure 3.	15
ADDITIONAL SUMMARY OF FINDINGS	19
DISCUSSION	25
AUTHORS' CONCLUSIONS	26
ACKNOWLEDGEMENTS	26
REFERENCES	26
CHARACTERISTICS OF STUDIES	29
DATA AND ANALYSES	50
Analysis 1.1. Comparison 1 Training versus no intervention, Outcome 1 Properly fitting RPE.	51
Analysis 2.1. Comparison 2 Conventional training plus additions versus conventional training, Outcome 1 Observed appropriate RPE use.	52
Analysis 2.2. Comparison 2 Conventional training plus additions versus conventional training, Outcome 2 Correct use of RPE as part of full-body PPE.	53
Analysis 2.3. Comparison 2 Conventional training plus additions versus conventional training, Outcome 3 Knowledge of RPE use at one-week follow-up.	54
Analysis 3.1. Comparison 3 Education versus no intervention, Outcome 1 Use of RPE most of the time.	55
Analysis 3.2. Comparison 3 Education versus no intervention, Outcome 2 Reported RPE use among farmers.	56
Analysis 3.3. Comparison 3 Education versus no intervention, Outcome 3 Using safety mask while working.	57
Analysis 3.4. Comparison 3 Education versus no intervention, Outcome 4 Use of RPE (PAPR).	57
Analysis 3.5. Comparison 3 Education versus no intervention, Outcome 5 Fit tested for N95.	58
Analysis 3.6. Comparison 3 Education versus no intervention, Outcome 6 Use of N95 mask.	58
Analysis 4.1. Comparison 4 Motivational interview-based education versus traditional lectures, Outcome 1 Use of RPE as part of full-body PPE.	59
ADDITIONAL TABLES	59
APPENDICES	62
CONTRIBUTIONS OF AUTHORS	71
DECLARATIONS OF INTEREST	71
SOURCES OF SUPPORT	71
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	72
INDEX TERMS	72

Behavioural interventions to promote workers' use of respiratory protective equipment

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ABSTRACT

Background

Respiratory hazards are common in the workplace. Depending on the hazard and exposure, the health consequences may include: mild to life-threatening illnesses from infectious agents, acute effects ranging from respiratory irritation to chronic lung conditions, or even cancer from exposure to chemicals or toxins. Use of respiratory protective equipment (RPE) is an important preventive measure in many occupational settings. RPE only offers protection when worn properly, when removed safely and when it is either replaced or maintained regularly. The effectiveness of behavioural interventions either directed at employers or organisations or directed at individual workers to promote RPE use in workers remains an important unanswered question.

Objectives

To assess the effects of any behavioural intervention either directed at organisations or at individual workers on observed or self-reported RPE use in workers when compared to no intervention or an alternative intervention.

Search methods

We searched the Cochrane Work Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL 2016, Issue 07), MEDLINE (1980 to 12 August 2016), EMBASE (1980 to 20 August 2016) and CINAHL (1980 to 12 August 2016).

Selection criteria

We included randomised controlled trials (RCTs), controlled before and after (CBA) studies and interrupted time-series (ITS) comparing behavioural interventions versus no intervention or any other behavioural intervention to promote RPE use in workers.

Data collection and analysis

Four authors independently selected relevant studies, assessed risk of bias and extracted data. We contacted investigators to clarify information. We pooled outcome data from included studies where the studies were sufficiently similar.

Main results

We included 14 studies that evaluated the effect of training and education on RPE use, which involved 2052 participants. The included studies had been conducted with farm, healthcare, production line, office and coke oven workers as well as nursing students and people with mixed occupations. All included studies reported the effects of interventions as use of RPE, as correct use of RPE or as indirect measures of RPE use. We did not find any studies where the intervention was delivered and assessed at the whole organization level or in which the main focus was on positive or negative incentives. We rated the quality of the evidence for all comparisons as low to very low.

Training versus no training

One CBA study in healthcare workers compared training with and without a fit test to no intervention. The study found that the rate of properly fitting respirators was not considerably different in the workers who had received training with a fit test (RR 1.17, 95% Confidence Interval (CI) 0.97 to 1.10) or training without a fit test (RR 1.16, 95% CI 0.95 to 1.42) compared to those who had no training. Two RCTs that evaluated training did not contribute to the analyses because of lack of data.

Conventional training plus additions versus conventional training alone

One cluster-randomised trial compared conventional training plus RPE demonstration versus training alone and reported no significant difference in appropriate use of RPE between the two groups (RR 1.41, 95% CI 0.96 to 2.07).

One RCT compared interactive training with passive training, with an information screen, and an information book. The mean RPE performance score for the active group was not different from that of the passive group (MD 2.10, 95% CI -0.76 to 4.96). However, the active group scored significantly higher than the book group (MD 4.20, 95% CI 0.89 to 7.51) and the screen group (MD 7.00, 95% CI 4.06 to 9.94).

One RCT compared computer-simulation training with conventional personal protective equipment (PPE) training but reported only results for donning and doffing full-body PPE.

Education versus no education

One RCT found that a multifaceted educational intervention increased the use of RPE (risk ratio (RR) 1.69, 95% CI 1.10 to 2.58) at three years' follow-up when compared to no intervention. However, there was no difference between intervention and control at one year's, two years' or four years' follow-up. Two RCTs did not report enough data to be included in the analysis.

Four CBA studies evaluated the effectiveness of education interventions and found no effect on the frequency or correctness of RPE use, except in one study for the use of an N95 mask (RR 4.56, 95% CI 1.84 to 11.33, 1 CBA) in workers.

Motivational interviewing versus traditional lectures

One CBA study found that participants given motivational group interviewing-based safety education scored higher on a checklist measuring PPE use (MD 2.95, 95% CI 1.93 to 3.97) than control workers given traditional educational sessions.

Authors' conclusions

There is very low quality evidence that behavioural interventions, namely education and training, do not have a considerable effect on the frequency or correctness of RPE use in workers. There were no studies on incentives or organisation level interventions. The included studies had methodological limitations and we therefore need further large RCTs with clearer methodology in terms of randomised sequence generation, allocation concealment and assessor blinding, in order to evaluate the effectiveness of behavioural interventions for improving the use of RPE at both organisational and individual levels. In addition, further studies should consider some of the barriers to the successful use of RPE, such as experience of health risk, types of RPE and the employer's attitude to RPE use.

PLAIN LANGUAGE SUMMARY

Ways to encourage workers to wear protective equipment to stop them breathing in harmful substances

It is common at many workplaces for the air to contain substances that are harmful to health. These may include bacteria and viruses, various fumes and smoke, and dusts and particles such as asbestos or grain. Depending on what and how much of it is inhaled, the health consequences may vary from mild to life-threatening. These consequences range from feelings of irritation to short- and long-

term illness including cancer. In many work settings respiratory protective equipment (RPE) is used to prevent workers from inhaling harmful substances. Various ways have been introduced to teach workers how to use RPE effectively. However it is unclear how well they work. Therefore, we wanted to find out if there are interventions that can encourage workers to use RPE correctly or more often.

Studies found

We searched for relevant research studies up to 20 August 2016. We found 14 studies that analysed the effectiveness of behavioural interventions to promote RPE use. We also located one ongoing study. Studies had been conducted with 2052 farm, healthcare, production line, office and coke oven workers as well as nursing students and people with mixed occupations. We did not find any studies where the researchers conducted and assessed an intervention at the level of a whole organization.

What the research says

All included studies compared different education and training interventions to encourage workers to use RPE correctly or more often. We found very low quality evidence that behavioural interventions such as education and training do not increase the number of workers that use RPE or that use RPE correctly.

What is the bottom line

We conclude that there is low to very low quality evidence that behavioural interventions do not encourage workers to use RPE correctly or more often. It is likely that our conclusions will change when new studies are published. We need better quality studies that look at the effectiveness of different types of interventions. These interventions should be targeted at both individuals and organisations, to improve effective RPE use. In addition, further studies should consider some of the barriers to the successful use of RPE, such as experience of health risk, types of RPE and the employer's attitude to RPE use.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Training versus no intervention						
Patient or population: Healthcare workers Settings: Veterans Affairs hospital, USA Intervention: Training Control: No intervention						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No intervention	Training				
Properly fitting RPE at 6 months follow-up (with fit testing)	806 per 1000	944 per 1000 (782 to 1000)	RR 1.17 (0.97 to 1.41)	83 (1 study)	⊕○○○ very low ¹	One Controlled Before After (CBA) study □
Properly fitting RPE at 6 months follow-up (with-out fit testing)	781 per 1000	906 per 1000 (742 to 1000)	RR 1.16 (0.95 to 1.42)	96 (1 study)	⊕○○○ very low ¹	One CBA-study □
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; □ Two studies Myers 1995 ; Or 2012 did not report enough data to be included in the analysis.						
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.						

¹ Starting at low quality, we downgraded the quality of evidence with one level because of small sample size. We would have downgraded the quality of evidence with one more level due to study limitations (only 1 CBA study with high risk of selection bias) but we had already reached very low quality. We found no reason to upgrade the quality of evidence.

BACKGROUND

The use of respiratory protective equipment (RPE) is an important preventive measure in many occupational settings. However, RPE only offers protection when worn properly, when removed safely and when it is either replaced or maintained regularly (Nicholson 2015).

Description of the condition

Respiratory hazards are common in the workplace. These hazards include biological agents, such as organisms that cause tuberculosis or influenza, vapours such as diisocyanates and welding fumes, and dusts and particles such as asbestos or grain. Respiratory hazards occur in a wide variety of occupations, including nursing, farming, construction, mining or work in the manufacturing industry.

Depending on the hazard and exposure, the health consequences may include mild to life-threatening illnesses from infectious agents, acute effects ranging from respiratory irritation to chronic lung conditions, or cancer from exposure to chemicals or toxins. For a workplace to be considered to have a significant inhalation hazard, employees must have been exposed to a respiratory hazard greater than a stipulated standard, such as the threshold limit value (TLV), as established by the American Conference of Governmental Industrial Hygienists (ACGIH) (Hubbard 2000).

Based on the so-called hierarchy of controls, employers should first try to eliminate, substitute or control the inhalation hazards through engineering controls (e.g. enhanced ventilation, isolation of equipment and products) (Ellenbecker 1996). If these are not feasible then administrative controls can be used (e.g. limiting exposure time by rotation of employees, limiting exposure time in set-up, final process or maintenance). RPE can be an additional intervention or sometimes the last line of defence.

RPE may also be used as an interim control measure because it is not immediately practical to implement some measures (such as engineering controls) when these hazards are present. In other situations RPE use may be appropriate when accessing a contaminated area for a short period, or when maintenance operations need to be carried out. In addition, RPE may need to be worn in some emergency situations.

In practice, the use of RPE is often favoured by employers because it is generally a cheaper option when compared to the cost of controlling the hazard at its source. In 2005, 40,002 private sector establishments were surveyed, having been randomly selected from 174,305 private sector establishments among 50 states or the District of Columbia of the United States (Doney 2005). Agricultural establishments employing 10 or fewer workers were excluded from this study. Doney 2005 found that RPE use was required in 4.5% of establishments and for 3.1% of employees. The US Occupational Safety & Health Administration (OSHA) respiratory protection standard covers an estimated five million respirator wearers working in an estimated 1.3 million workplaces

in the covered sectors (OSHA 1998). The major limitation of RPE is that the anticipated protection is achieved only if the equipment is worn correctly. In addition, RPE performance in the workplace is generally much poorer than is suggested by standards or manufacturers' literature (Howie 2005).

Description of the intervention

It is not possible to control exposure by simply providing RPE to workers. RPE can only be effective if used as part of a more comprehensive programme (Szeinuk 2000). Howie 2005 gives the following definition of an RPE programme that should only be used after all technically possible controls have been implemented:

- workers who still need respiratory protection should be identified;
- workers should be informed of the consequences of exposure to ensure that they correctly understand the importance of wearing respiratory protection;
- the correct protective equipment, which can adequately control residual exposure, should be selected;
- the protective equipment should be matched to the wearer on an individual basis and with fit tests. It should be ensured that when more protective equipment is used at the same time, they are mutually compatible and that there are no other risks created (e.g. impairment of the visual field);
- the wearer should be trained and supervised;
- efforts should be made to minimise wearing times and equipment should be maintained in an efficient and hygienic condition;
- there should be a monitoring programme to ensure continuing effectiveness of the respiratory protection programme.

In many countries there are legal requirements for the use of respiratory protection that make one or more of these elements mandatory (OSHA 1998). For example, see Directive 89/656/EEC 1989 on the use of personal protective equipment (PPE), of which RPE use is an integral part.

Many workplaces where RPE is used do not have a written programme to determine the type of respirator to use. In addition, in many workplaces staff either do not know RPE is required, or employees are not assessed for medical fitness to wear RPE (Han 2009). In more than 20% of workplaces surveyed in the United States, staff were unaware of whether air sampling was performed for respiratory hazards to which the workers were exposed, respirator training was not provided for workers and programme administrators had not received respirator training (Greskevitch 2007). Training is essential because proper functioning depends to a great extent on wearing the equipment correctly (Howie 2005).

There are also distinct barriers to the use of RPE. A study of firefighters in the United States reported that lack of funding (48%) and lack of understanding (39%) were the greatest barriers to

programme implementation (Easterling 2007). Salazar 2001 describes the factors that had the most positive influence on respirator use, which were concern about work exposure, fit test and training, while the factors that were the most negative influences were communication, personal comfort, effect on vision, structural environment and fatigue.

Other studies have reported the benefit of various types of RPE to prevent the intake of various hazardous substances into the body via inhalation, but many of these studies do not address the personal behaviour of the workers and their actual use of RPE while they are at work (Malo 1992; Oguss 2010; Syamlal 2007; Vigo 2005).

How the intervention might work

The purpose of RPE is to prevent the inhalation of harmful airborne substances or to provide a source of breathable air when breathing in oxygen-deficient atmospheres. This is achieved in workplaces by means of training, fit testing and supervision of the correct wearing of RPE, including all the programme elements mentioned above.

RPE programmes can be implemented at several levels. The first is implementation of a programme at a national level. In many countries there is legislation in place that makes it mandatory for employers to have such a programme under certain conditions. Compliance with legislation can be voluntary, enhanced by incentives such as money or prizes/awards for the best complying organisations or enforced by agencies such as a Labour Inspectorate. At the company level, policies and employer support for RPE programmes can be encouraged by incentives and disincentives. At the individual level, it is often the individual worker's behaviour that determines whether RPE is maintained, worn and worn correctly. Individual RPE compliance is a multi-component, behavioural process. Various factors affect RPE use at different stages of compliance, for example workers' perception of risks, ease of use and how comfortable or uncomfortable it is to use the RPE. These are potential leverage points.

Training is important but needs to go beyond basic knowledge. Facilitating or enabling the conditions and workplace climate enhance the transfer of training and are important for day-to-day ongoing compliance.

Why it is important to do this review

Lunt 2011 reviewed the effects of behavioural interventions for dermal and respiratory hazards but the interventions reviewed were focused on a wider array of behaviour than just RPE use. Furthermore, they did not use Cochrane methods for their review. There are no systematic reviews of the effectiveness of behavioural interventions that are either directed at organisations or directed at

individual workers to promote RPE use in workers. Consequently this remains an important unanswered question.

OBJECTIVES

To assess the effects of any behavioural intervention either directed at organisations or at individual workers on observed or self-reported RPE use in workers when compared to no intervention or an alternative intervention.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs). We included trials where the intervention was assigned either to individual participants or clusters of participants.

It is difficult to randomise in a work organisation. Therefore we also included non-randomised studies. We considered the following non-RCT study designs for inclusion: controlled trials without randomisation, such as controlled before and after (CBA) studies where the outcome was measured before and after the intervention, and interrupted time-series (ITS), which refers to multiple observations of the outcome over time that were 'interrupted' by an intervention or treatment.

In future updates of this review, we will include ITS studies that have at least three data points before and three data points after the interrupting intervention (EPOC 2006; Ramsay 2003).

Types of participants

Workers exposed to respiratory hazards that require RPE use.

Types of interventions

- Behavioural interventions directed at organisations aiming to implement RPE programmes.

We categorised these interventions as:

- legislation and enforcement;
- incentives, as in money or positive feedback; and
- information and guidance.

- Behavioural interventions directed at workers for promoting RPE use.

We categorised these interventions as:

- information, education and training;

- incentives, as in money or positive feedback;
- sanctions and negative feedback.

We compared any intervention with alternative interventions or no intervention.

Types of outcome measures

Primary outcomes

- For organisations: proper implementation of all elements of an RPE programme.
- For workers: appropriate use of RPE. We studied both short-term behavioural outcomes immediately after the intervention and long-term behavioural outcomes more than six months after the intervention. We considered both self-reports and observations of RPE use as equally valid. We made a distinction between the measurement of using RPE as such and properly fitting RPE and reported these as separate outcomes.

Secondary outcomes

- Degree to which barriers to RPE use had been overcome.
- Degree to which RPE use hinders normal functioning at work.

We only included studies if they had measured our primary outcome criteria and we use only the primary outcomes for drawing conclusions about the effectiveness of the interventions.

Search methods for identification of studies

Electronic searches

We searched the following databases: CENTRAL (first in 2013, Issue 11 and last in 2016 Issue 07), which includes the Cochrane Work Group Specialised Register of trials, MEDLINE (1980 to August 12, 2016), EMBASE (1980 to August 20, 2016) and CINAHL (1980 to August 12, 2016). We also searched Dissertation Abstracts to identify additional studies on respiratory protection that may not necessarily appear in the published literature. There were no restrictions on language, date or place of publication.

The search strategy we used for MEDLINE through PubMed is included as [Appendix 1](#). We developed search strategies for the other databases based on the MEDLINE strategy. We present the search strategies for the other databases as [Appendix 2](#), [Appendix 3](#) and [Appendix 4](#).

We also wanted to find non-randomised studies. Therefore we did not apply a study design filter but we only used search strings for RPE and work.

Searching other resources

We scrutinised the reference lists of identified study reports for additional citations. We contacted specialists in the subject area about unpublished data.

Data collection and analysis

The methodology for data collection and analysis is based on the *Cochrane Handbook of Systematic Reviews of Interventions* ([Higgins 2011](#)).

Selection of studies

Four authors (YT, HM, PS and DK) independently screened references identified by the systematic searches to identify articles that would fulfil our inclusion criteria. Where there was disagreement or doubt, we retrieved the full article. These same four authors (YT, HM, PS and DK) independently assessed the full study report to see if it met the review inclusion criteria. We consulted the remaining review author (ML) in cases of unresolved disagreement. Then, based on full-text assessment, we included all studies that fulfilled the inclusion criteria as described above in [Criteria for considering studies for this review](#).

Data extraction and management

Four authors (YT, HM, PS and ML) independently extracted data about the methods, participants, interventions, outcomes and main results of the included trials using a data collection form. We consulted the fifth author (DK) in cases of unresolved disagreement. Where necessary, we contacted the trial authors directly to complete data forms or clarify methodology. We entered the extracted data into the Cochrane statistical software, Review Manager ([RevMan 2014](#)), and checked them for accuracy.

Assessment of risk of bias in included studies

Four review authors (YT, HM, DK and ML) independently conducted 'Risk of bias' assessment of all the included studies by adapting the procedures described for the six domains in the Cochrane Handbook for Systematic Reviews of Interventions ([Higgins 2011](#)): random sequence generation, allocation concealment, blinding of outcome assessors, incomplete outcome data, selective reporting and other potential sources of bias. We graded each study for risk of bias in each domain, with ratings of low risk of bias, high risk of bias or uncertain risk of bias.

We judged a study to have a low overall risk of bias when we judged that all of the aforementioned criteria were at low risk of bias. Conversely, we considered a study to have a high overall risk of bias if we judged that any of the aforementioned criteria were at high or unclear risk of bias.

We resolved disagreements by discussion.

If we include any interrupted time-series (ITS) studies in future updates of this review, we will assess their risk of bias with the criteria developed by the Cochrane Effective Practice and Organisation of Care (EPOC) Group (EPOC 2006).

The quality assessment for ITS designs consists of:

- protection against secular changes (three items);
- protection against detection bias (two items);
- completeness of data set (one item); and
- reliable primary outcome measures (one item).

We will answer each item as 'done', not clear' or 'not done'.

Measures of treatment effect

We plotted the results of each RCT as point estimates, such as risk ratios (RRs), indicating change in binary outcomes such as appropriate use of RPE (yes/no), and means and standard deviations (SDs) for continuous outcomes such as frequency of appropriate use of RPE.

For controlled studies with baseline differences and continuous outcome measures, we took the changes between baseline and follow-up as the measure of treatment effect. With dichotomous outcome measures we plotted both the outcomes at baseline and at follow-up as rate ratios.

If we include any ITS studies in future updates of this review, we will extract data from the original papers when available and re-analyse them according to the recommended methods for analysing ITS designs for inclusion in systematic reviews (Ramsay 2003).

Unit of analysis issues

We included studies where individual workers were randomised and also cluster-randomised studies (CRT) where, for example, workplaces were the unit of randomisation. For studies that employed a cluster-randomised design but did not make an allowance for the design effect we calculated the design effect based on a fairly large assumed intra-cluster correlation of 0.10. We based this assumption by analogy on studies about implementation research (Campbell 2000; Ukoumunne 1999). We followed the methods in the *Cochrane Handbook for Systematic Reviews of Interventions* for these calculations (Higgins 2011).

Dealing with missing data

We contacted authors to obtain missing data from their reports that were needed for meta-analysis. We received data from Perry 2003. In the updates of this review, if statistics are missing, such as standard deviations or correlation coefficients, we will calculate them from other available statistics such as P values according to the methods in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of heterogeneity

We assessed clinical homogeneity based on similarity of population, intervention, outcome and follow-up (Verbeek 2012). We considered interventions to be similar if they fell into one of the pre-defined categories of interventions (as stated in [Criteria for considering studies for this review](#)) and had similar content. We made a distinction between education only and education that included demonstration and fitting of RPE because we expected that demonstration and fitting would increase the effect of instruction. We added another category that we described as multifaceted interventions, which combined elements of the various intervention types.

We considered a no intervention control group different from one in which a minor intervention was applied.

We regarded the outcomes use of RPE and the correctness of the fit of RPE to be different and we did not combine them. We regarded follow-up times of less than three months, three months to one year and more than one year as different.

We regarded healthcare workers exposed to tuberculosis bacteria as being different from farm workers exposed to organic dust and we did not combine these studies.

If we can pool studies in future updates of this review, we will test for statistical heterogeneity by means of the Chi² test as implemented in the forest plot in RevMan 2014. We will use a significance level of P value < 0.10 to indicate whether there is a problem with heterogeneity. Moreover, we will quantify the degree of heterogeneity using the I² statistic, where an I² value of 25% to 50% indicates a low degree of heterogeneity, 50% to 75% a moderate degree of heterogeneity and > 75% a high degree of heterogeneity (Higgins 2003).

Assessment of reporting biases

We prevented reporting bias by including studies and not publications in order to avoid the introduction of duplicate data (i.e. two articles could represent duplicate publications of the same study). Following the Cho 2000 statement on redundant publications, we attempted to detect duplicate studies and, if more articles had reported on the same study, we would have extracted the data only once. We prevented location bias by searching across multiple databases. We prevented language bias by not excluding articles based on language. As we did not have more than five studies to include in a single comparison, we did not assess publication bias by using a funnel plot.

Data synthesis

We pooled studies that were sufficiently similar with RevMan 5.3 software (RevMan 2014). When studies were not statistically heterogeneous we used a fixed-effect model.

GRADE and 'Summary of findings'

We used the GRADE approach as described in the *Cochrane Handbook for Systematic Reviews of Interventions*, using the GRADEPro 3.2 software to present the quality of evidence in a 'Summary of findings' table (GRADEpro 2008; Higgins 2011).

The downgrading of the quality of a body of evidence for a specific outcome is based on five factors:

- study limitations;
- indirectness of evidence;
- inconsistency of results;
- imprecision of results;
- publication bias.

The GRADE approach specifies four levels of quality (high, moderate, low and very low).

We report the findings for the four training and education intervention categories and the primary outcomes in four summary of findings tables. We do not report the secondary outcomes there because studies using these outcomes form only a subset of all available studies, as per our inclusion criteria.

Subgroup analysis and investigation of heterogeneity

We did not conduct subgroup analysis as there were so few studies to include. In the future updates of this review we will carry out subgroup analyses for the primary outcomes. If sufficient data are available, we will conduct the subgroup analyses according to the following factors:

- type of work: different sectors of work (e.g. health care, farming);
- category of behavioural interventions (e.g. training versus behaviour-based safety versus organisational-level (safety climate/culture interventions));
- types of RPE: full versus partial RPE;
- gender;
- high versus low exposure area.

Sensitivity analysis

We would have carried out sensitivity analysis to explore the effect of study risk of bias but there were too few studies available per comparison.

RESULTS

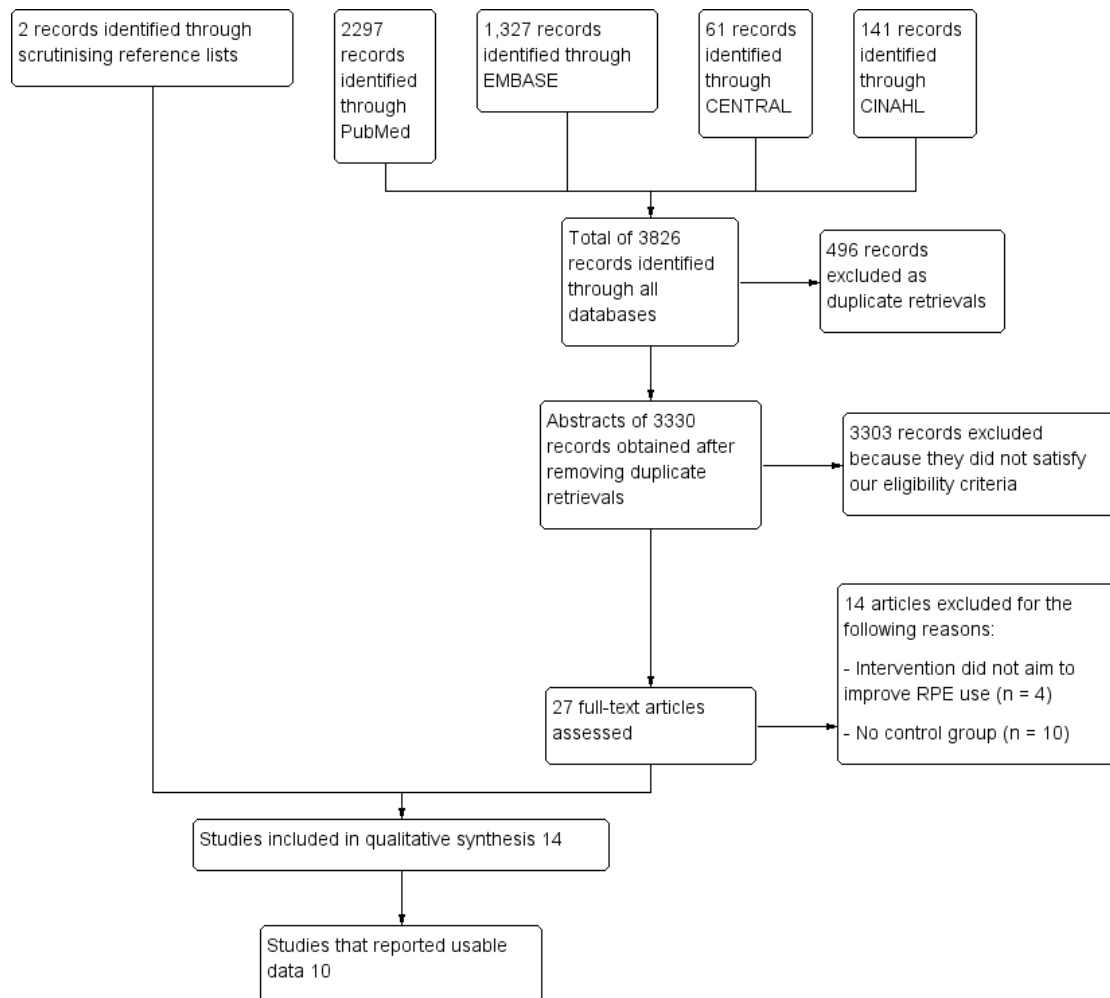
Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

We conducted our systematic search in December 2013 and again in August 2016. We identified 3826 records from four databases (CENTRAL, PubMed, EMBASE, CINAHL). After excluding 496 duplicate records, we were left with 3330 records for screening of titles and abstracts according to the eligibility criteria. We conducted additional searches in Dissertation Abstracts but there were no studies that satisfied our inclusion criteria. Screening of all the de-duplicated records produced only 27 potentially eligible studies to retrieve as full-text articles that we considered for inclusion. We also checked the reference lists of these potential included studies and found no further potential studies to include. We identified two further potential studies from a systematic review addressing a topic related to our review (Lunt 2011). Having read all 29 full-text articles, we excluded 14 studies. Finally, we included 14 studies in this review that satisfied our inclusion criteria. In addition, we located one ongoing study. See [Figure 1](#) for a PRISMA study flow diagram showing a detailed account of the search and study inclusion process.

Figure 1. PRISMA flow chart of study selection procedure



Included studies

We included 14 studies. One study is still ongoing ([Chen 2016](#)) and we present it in [Characteristics of ongoing studies](#). Full details of the other 14 studies are presented in the [Characteristics of included studies](#) table.

Design of the studies

Of the 14 published studies, eight were RCTs ([Carrico 2007](#); [Donham 2011](#); [Eckerman 2002](#); [Hung 2015](#); [Myers 1995](#); [Or 2012](#); [Parkinson 1989](#); [Perry 2003](#)), and six were CBA studies ([Dressel 2007](#); [Gjerde 1991](#); [Hannum 1996](#); [Kim 2012](#); [Navidian 2015](#); [Shamsi 2015](#)). [Carrico 2007](#) randomised healthcare workers but measured the

use of RPE at the patient level and therefore there was clustering at the healthcare worker level. We considered this to be a cluster-randomised trial. We therefore adjusted for the clustering effect according to the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We adjusted the results for the clustering based on a calculated design effect $(1 + (4.2 - 1) * 0.1 = 1.32)$. We used this design effect as a correction factor for dividing the events and the number of participants. The average cluster size of 4.2 was based on a total of 84 observations for the 20 nurses studied. The intra-cluster correlation (ICC) of 0.1 is a conservative estimate based on analogy with implementation interventions and taken from [Campbell 2000](#). Even though farms were randomised in [Donham 2011](#), there was only one participant per farm and we did not consider this a cluster-randomised trial. [Parkinson 1989](#) used a cluster-randomised design comparing workers randomly

chosen from seven intervention plants with workers randomly chosen from control plants. The intervention was randomly assigned to the intervention plant group. There was no adjustment for the clustering effect. However, because the authors did not report sufficient data we could not calculate an adjusted effect estimate. The included CBA studies used a variety of intervention and control groups. [Gjerde 1991](#) conducted an educational intervention study with swine confinement producers in Iowa. The swine confinement workers from seven southeastern counties were designated as the educational intervention (or treatment) group. Workers from seven northeastern counties served as the non-intervention (or control) group. [Hannum 1996](#) conducted a trial with two intervention groups of individual and group training and a control group without training. [Dressel 2007](#) compared an intervention group consisting of farmers with a control group, where they simply stated that they “did not participate”. It is unclear if these were farmers that were not willing to participate in the intervention or if there were other reasons for non-participation.

Study settings and time

Eight studies were carried out in the USA. The other six studies were conducted outside the USA: one in Canada ([Kim 2012](#)), one in Germany ([Dressel 2007](#)), two in Iran ([Navidian 2015](#); [Shamsi 2015](#)), and two in Hong Kong ([Hung 2015](#); [Or 2012](#)). The publication dates of the studies spanned 23 years, with one in the 1980s ([Parkinson 1989](#)), and three in the 1990s ([Gjerde 1991](#); [Hannum 1996](#); [Myers 1995](#)). Ten studies were carried out after 2000 ([Carrico 2007](#); [Donham 2011](#); [Dressel 2007](#); [Eckerman 2002](#); [Hung 2015](#); [Kim 2012](#); [Navidian 2015](#); [Or 2012](#); [Perry 2003](#); [Shamsi 2015](#)).

Participants and duration of studies

Altogether the 14 included studies involved 2052 participants. Four studies involved healthcare workers ([Carrico 2007](#); [Hannum 1996](#); [Hung 2015](#); [Or 2012](#)). The healthcare workers were 20 emergency department registered nurses in [Carrico 2007](#), 179 healthcare workers employed in a 775-bed Veterans’ Affairs hospital in [Hannum 1996](#), 50 registered nurses, enrolled nurses and healthcare assistants in [Hung 2015](#) and 84 first-year undergraduate nursing students in [Or 2012](#). Follow-up time was three months (from January to March 2005) in [Carrico 2007](#) and two years in [Hannum 1996](#), but it was unclear at what time during follow-up the outcome was measured. Different follow-up times were found in [Hung 2015](#) (one week for the control group and two weeks for the intervention group). [Or 2012](#) provided unclear information on follow-up time.

Five studies involved farm workers ([Donham 2011](#); [Dressel 2007](#); [Gjerde 1991](#); [Kim 2012](#); [Perry 2003](#)). [Donham 2011](#) included various farms (308). [Dressel 2007](#) evaluated the effects of the intervention in 105 farmers with occupational asthma. [Gjerde 1991](#)

studied 209 swine confinement workers, [Kim 2012](#) involved 68 farmers and [Perry 2003](#) studied 400 Wisconsin dairy farmers certified to apply pesticides to field crops over a one-year evaluation period. Follow-up times in these studies varied from one month to four years.

Five studies involved other types of workers ([Eckerman 2002](#); [Myers 1995](#); [Navidian 2015](#); [Parkinson 1989](#); [Shamsi 2015](#)). [Eckerman 2002](#) involved 123 adults recruited through advertisements in local newspapers, the website of the Oregon Health and Science University and flyers distributed at a liberal arts university. [Myers 1995](#) studied 64 white-collar workers who were not engaged in the research, design or manufacture of RPE and were inexperienced in RPE use. [Navidian 2015](#) studied 70 workers at glass production facilities. [Parkinson 1989](#) involved 328 coke oven workers from seven pairs of coke plants, matched regarding geographic location, work force size and ethnic composition. [Shamsi 2015](#) involved 44 construction workers building subway stations. Follow-up times in these studies varied from three days to six months.

Types of intervention and comparison groups

Interventions directed at organisations

We did not find any studies where the intervention was delivered and assessed at the whole company level. We had expected to find studies that had evaluated the effectiveness of legislation and enforcement, incentives such as money or positive feedback, or information and guidance. However, we found no such studies.

Interventions directed at workers

All 14 included studies evaluated only training and education interventions. Following the example of [Cheetham 2016](#), we defined training as the imparting or shared practice of skills and education as the imparting or shared creation of knowledge. When it comes to learning how to use RPE, training involves participants handling the equipment themselves, which means putting it on, taking it off and adjusting it. We classified six studies as training interventions. Education on the other hand involves class lectures or presentations, group-based instruction or other types of information delivery such as leaflets and self-learning packages. We classified the remaining eight included studies as education interventions. We present the details of each intervention in [Table 1](#). We present the results of training and education interventions separately in the four following comparisons.

1. Training versus no intervention

There were only two studies comparing training with no intervention ([Hannum 1996](#); [Or 2012](#)). In the [Hannum 1996](#) study the

intervention groups received one-on-one training by the hospital hygienist and the respirators were fit tested. Another group received group instruction on the ward, and the third group received no formal training. The control group had none of these interventions. In [Or 2012](#), there were three educational groups: group A was trained in fit check procedure and fit test performance, group B did not perform fit test but was trained in fit check procedure, and group C received fit test performance but no training in fit check procedure. Group D served as a control group with no fit test performed and was not trained to perform the fit check.

2. Conventional training plus additions versus conventional training alone

There were four studies comparing conventional training plus additions with conventional training alone ([Carrico 2007](#); [Eckerman 2002](#); [Hung 2015](#); [Myers 1995](#)). In the [Carrico 2007](#) study, the intervention group received supplemental training in addition to classroom training, using visual demonstration of respiration particle dispersion involving the use of a patient bio-simulator. The control group received standard classroom teaching. [Eckerman 2002](#) had four groups of intervention: programmed instruction (PI) active, PI passive, INFO-book (reading information from a book, non-interactive) and INFO-screen (reading information on a computer screen, non-interactive). The intervention provided basic respiratory protection information and addressed the following: uses (preventing symptoms), limitations (immediately dangerous to life or health conditions, seal, fit tests), and maintenance of air-purifying and supplied air respirators (valve, cartridge replacement); recognition of respiratory hazards (lead, solvents, carbon monoxide; acute and chronic effects); selection of proper respirators for different hazards (material safety data sheets, product labels, permissible exposure limits) and measurement of hazard levels. In [Hung 2015](#) the intervention group received conventional personal PPE training plus computer-simulated training using the proposed simulation program - web-based interactive software with a user-friendly graphical interface for users to practise the use of PPE via dragging and dropping various PPE onto a virtual healthcare worker and by responding to multiple choice questions online. The control group received conventional PPE training only. In [Myers 1995](#) the intervention group was trained to don the RPE with the aid of a fit check, while the control group was trained to don the RPE without conducting a fit check.

3. Education versus no intervention

There were seven studies comparing education with no intervention ([Donham 2011](#); [Dressel 2007](#); [Gjerde 1991](#); [Kim 2012](#); [Parkinson 1989](#); [Perry 2003](#); [Shamsi 2015](#)). The [Donham 2011](#) study employed a multifaceted intervention that included medical

screening, education, on-farm safety audits with set safety standards and performance incentives. A USD 200 monetary incentive was given to participants if they had more than 85% compliance on an audit score including RPE use. The intervention was given to the principal operator of the farm. The control group received no intervention. [Dressel 2007](#) used two sessions that lasted four to five hours to explain the causes and prevention of occupational asthma and to demonstrate the use of respirators. In the [Gjerde 1991](#) study, the participants in the intervention group received a series of six educational home study modules and were invited to attend one of three evening sessions in which respirator use and gas measurement were demonstrated. The control group was reported as non-intervention without any further details. [Kim 2012](#) provided one evening of education on work-related asthma and agricultural causes; spirometry testing; respirator demonstrations and fit testing; exposure reduction strategies; and barriers to personal protective equipment (PPE) use, whereas the control group received no intervention. [Parkinson 1989](#) used four sessions during a two-year period with information about the occupational safety and health work of the unions, cancer risk at the coke plant, the Occupational Safety & Health Administration (OSHA) coke oven standard and the content of the control programme at each plant. The control group received no intervention. [Shamsi 2015](#) distributed a free package containing a well-designed, light-weight helmet, a dust mask, safety gloves and a simple tailored pamphlet about the advantages of using PPE and the risks they can reduce to the intervention group. A sticker with an emotionally tailored message reminding participants of the importance of caring for themselves because of their families was attached to the helmet. The control group received no intervention. In the study by [Perry 2003](#), the intervention group received three hours of education sessions targeting four messages, including (1) existing evidence of excess cancers among farmers; (2) simulation of pesticide exposure presented through a slide show and description; (3) feedback on self-reported data collected from the farmers to date, and (4) cognitive behavioural strategies that could be adopted to reduce pesticide hazards and ultimately cancer risks. The intervention also included a training component that gave participants the opportunity to try on RPE, practice a brief check to make sure that all parts of the body were covered, and timing each other to illustrate how one can gear up properly in only a few minutes. In effect, the intervention contained both education and training components but education formed the bulk. The control group attended the standard re-certification meeting. The education sessions were given in groups ranging between 20 and 50 applicators (the term used by the study authors to denote participants).

4. Motivational interview-based education versus traditional lectures

[Navidian 2015](#) gave the intervention group four educational sessions based on motivational interviewing, which were conducted

in four groups of eight to 10 participants. Participants in the control group attended four one-hour safety education sessions given in the form of traditional lectures.

Sanctions

We found no studies that evaluated the effectiveness of sanctions, such as fines or negative feedback on RPE use.

Types of outcome measures

There were basically two types of eligible outcome measures: use of RPE and the correct use of RPE as measured by a fit test. The included studies reported results on either of these outcomes as follows:

Use of RPE

In the [Carrico 2007](#) study the outcome of interest was the use of PPE including self-use of the mask and placement of the mask on the patient as observed by two trained observers. The specific type of RPE was a N95 respirator. We measured the RPE outcome from the self-use of the mask and placement of the mask. [Donham 2011](#) measured self-reported respirator use at baseline and at one, two and three years of follow-up. [Dressel 2007](#) measured RPE used. However, the specific type of RPE in this study was head gear. [Gjerde 1991](#) presented self-reported use of an appropriate dust mask or some type of respirator when working at baseline and one year later using a questionnaire. [Kim 2012](#) reported the use of PPE, including reported mask use, use of a N95 mask, fit-testing for N95, use of respirator (powered air purifying respirator), and use of mask while brushing animals. These outcomes were related to RPE. [Parkinson 1989](#) used 'wearing respirator always' to indicate RPE use. [Shamsi 2015](#) measured self-reported use of PPE, including the use of helmet, safety mask, safety gloves and safety shoes while working. We considered using a safety mask while working to be RPE use.

Correct use of RPE

[Hannum 1996](#) reported the correct use of RPE as measured by passing a respirator fit test administered by nurses at six months after the intervention. [Myers 1995](#) measured successful RPE donning tested over three days immediately after training. The authors measured the quality of each donning from measurements

of particle concentrations inside and outside the respirator during a chamber test. [Or 2012](#) measured respirator fit continuously for a period of 15 minutes.

Three included studies measured RPE use as part of full-body protection (PPE) use ([Hung 2015](#); [Navidian 2015](#); [Perry 2003](#)) and we could not separate RPE use from PPE use. [Hung 2015](#) reported mean scores of performance in PPE donning and doffing at pre- and post-intervention. An N95 respirator was a part of the PPE but its specific appropriate use data were not reported. [Navidian 2015](#) reported the safety awareness, attitude and performance on the use of PPE. The authors measured PPE performance at pre- and post-intervention with a checklist with seven items concerning the use of any suitable equipment with a respirator being one of them. The authors did not report specific scores for RPE use. [Perry 2003](#) measured self-reported compliance with full PPE including a respirator. However, we could not extract the specific information on respirator use from the PPE compliance outcome. We consider these three studies to yield indirect evidence of effectiveness regarding correct use of RPE.

One included study evaluated correct use of RPE in a fashion that we did not foresee in our protocol ([Sakunkoo 2012](#)), by measuring knowledge regarding the correct use of RPE [Eckerman 2002](#). This is of course not the same as skill in actually using RPE. The authors reported performance scores for basic respiratory protection information measured by a quiz test that contained four-item multiple-choice questions. We consider this study providing indirect evidence of effectiveness regarding correct use of RPE.

Excluded studies

We excluded 14 studies ([Adewoye 2014](#); [Bailey 2010](#); [Becker 2004](#); [Casalino 2015](#); [Contreras 2012](#); [Crippa 2007](#); [Fu 2013](#); [Gershon 2009](#); [Harber 2013](#); [Harber 2014](#); [Huaroto 2013](#); [Jenkins 2007](#); [Myong 2016](#); [Woith 2015](#)). Reasons for the exclusion of these studies are presented in the [Characteristics of excluded studies](#) table.

Risk of bias in included studies

We present our judgements about each risk of bias item as percentages across all included studies in [Figure 2](#), whereas [Figure 3](#) shows our judgements about each risk of bias item for each included study.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

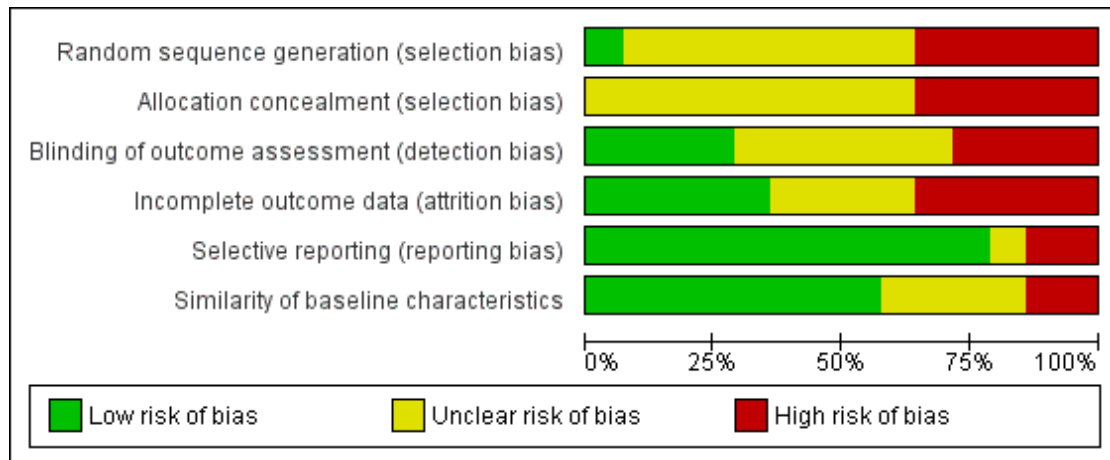


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Similarity of baseline characteristics
Carrico 2007	?	?	+	+	+	+
Donham 2011	?	?	+	-	+	+
Dressel 2007	-	-	-	?	+	-
Eckerman 2002	?	?	?	-	+	?
Gjerde 1991	-	-	-	-	+	+
Hannum 1996	-	-	+	+	+	?
Hung 2015	?	?	?	+	+	+
Kim 2012	-	-	-	-	+	-
Myers 1995	?	?	?	?	?	?
Navidian 2015	?	?	?	?	+	+
Or 2012	?	?	?	?	-	+
Parkinson 1989	?	?	?	-	-	?
Perry 2003	+	?	+	+	+	+
Shamsi 2015	-	-	-	+	+	+

Allocation

One RCT reported having used computer-generated allocation and therefore we judged it to have a low risk of bias for this item (Perry 2003). However, Perry 2003 did not describe allocation concealment and so we judged the study to have an unclear risk of bias for this item. The other eight included RCTs did not report their methods of sequence generation or allocation concealment (Carrico 2007; Donham 2011; Eckerman 2002; Hung 2015; Myers 1995; Navidian 2015; Or 2012; Parkinson 1989). Therefore, we judged the risk of selection bias to be unclear for these studies.

The other five trials were controlled before and after studies (Dressel 2007; Gjerde 1991; Hannum 1996; Kim 2012; Shamsi 2015). We assessed their potential for selection bias from the domain of similarity of baseline characteristics. Gjerde 1991 and Shamsi 2015 showed no significant differences in demographic characteristics of the intervention and control groups. We judged the risk of selection bias to be low. Hannum 1996 reported no information on baseline characteristics. We judged the risk of selection bias to be unclear. Dressel 2007 and Kim 2012 both had substantial differences in their baseline characteristics and we judged them to be at high risk of selection bias.

Blinding

We only assessed blinding of outcome assessors because blinding of participants is not feasible for behavioural interventions. We found that outcome assessors were blinded in four studies (Carrico 2007; Donham 2011; Hannum 1996; Perry 2003). Therefore we judged them to have a low risk of bias for this item. Gjerde 1991, Dressel 2007, Kim 2012 and Shamsi 2015 reported using a self-administered questionnaire for outcome assessment. We therefore judged the risk of detection bias to be high. We judged the other six studies to be at unclear risk as there was no information available on blinding (Eckerman 2002; Hung 2015; Myers 1995; Navidian 2015; Or 2012; Parkinson 1989).

Incomplete outcome data

We judged five studies to have a low risk of attrition bias (Carrico 2007; Hannum 1996; Hung 2015; Perry 2003; Shamsi 2015). Carrico 2007, Hannum 1996; Hung 2015 and Shamsi 2015 reported all outcome data in all recruited participants. Perry 2003 reported only 6% and 3% dropouts in the intervention and control groups, respectively.

We judged five studies to have a high risk of attrition bias because of high loss to follow-up overall or because participant attrition was not the same for intervention and control groups (Donham 2011; Eckerman 2002; Gjerde 1991; Kim 2012; Parkinson 1989).

Donham 2011 recruited 308 farmers (150 CSF intervention farmers and 158 controls), but there were altogether 281 farmers (91.2%), meaning 141 CSF intervention farms and 140 controls in the analysis for respirator use at entry. Considerable numbers of farmers dropped out from the study every year. At the fourth year of follow-up results were reported only for 75 farmers (50.0%) in the CSF intervention group and 55 farmers (34.8%) in the control group. Eckerman 2002 reported 36% (44/123) overall loss to follow-up, which means that 13/32 dropped out from the PI active group, 11/32 dropped out from the PI passive group, 8/28 dropped out from the INFO-book group and 12/32 dropped out from the INFO-screen group. In Gjerde 1991, data appropriate for the chosen analyses were obtained from 49 out of 102 workers in the intervention group and 79 out of 107 workers in the control group. In that study, 75% and 67% of all workers in the intervention group provided useful information at baseline and at one-year follow-up, while in the control group 88% and 80% of all workers in the control group provided useful information at baseline and at one-year follow-up. Kim 2012 reported that 76% (29/38) of the intervention group and 77% of the control group completed the follow-up survey at six months after the intervention. Parkinson 1989 included 554 workers but analysed 68% of these and did not adjust for missing data.

In the remaining four studies information to judge attrition was insufficient and therefore we judged the studies to have an unclear risk of attrition bias. (Dressel 2007; Myers 1995; Navidian 2015; Or 2012).

Selective reporting

We judged 11 studies to have a low risk of reporting bias as they reported data for all the outcome measures they listed in their methods (Carrico 2007; Donham 2011; Dressel 2007; Eckerman 2002; Gjerde 1991; Hannum 1996; Hung 2015; Kim 2012; Navidian 2015; Perry 2003; Shamsi 2015). We judged two studies to have a high risk of reporting bias (Or 2012; Parkinson 1989). Or 2012 did not present the expected outcomes clearly and in Parkinson 1989 the authors did not report all the same data at follow-up as they did at baseline.

Other potential sources of bias

In Donham 2011, farms that achieved at least an 85% audit score were awarded Certified Safe Farm status and were considered to be in the intervention group. These farms were also given a small financial incentive.

The self-reporting of outcomes in Gjerde 1991, in which participants were volunteers selected from among those farms eligible to participate, may give rise to the risk of a social desirability bias.

Hannum 1996 mentioned that the project started with participants being taught by the industrial hygienist (Group A). They later introduced group teaching by nurses (Group B) when the progress of individual training was not quick enough for the hospital. Subsequently, these groups were qualitatively fit-tested, together with those remaining who had not received training (Group C). This ad hoc arrangement may have led to selection bias.

Overall risk of bias

None of the included studies had low risk of bias for all items, which was our criterion for determining low overall risk of bias per study (see [Assessment of risk of bias in included studies](#)). We judged only one RCT to come close in that it had a low risk of bias in all but one domain (allocation concealment) (Perry 2003). Consequently we judged all included studies to have a high overall risk of bias.

Effects of interventions

See: [Summary of findings for the main comparison Training versus no intervention](#); [Summary of findings 2 Conventional training plus additions versus conventional training](#); [Summary of findings 3 Education versus no intervention](#); [Summary of findings 4 Motivational interview-based education versus traditional lectures](#)

We could report results data only for the primary outcomes of use of respiratory protective equipment (RPE) and correct use of RPE from 13 of the included studies (Carrico 2007; Donham 2011; Dressel 2007; Gjerde 1991; Hannum 1996; Hung 2015; Kim 2012; Myers 1995; Navidian 2015; Or 2012; Parkinson 1989; Perry 2003; Shamsi 2015). Three of these reported the effect of their interventions on the correct use of full-body protective equipment of which RPE was just one part (Hung 2015; Navidian 2015; Perry 2003).

The single remaining study reported data for knowledge of the correct use of RPE, which we accepted as a proxy measure of correct use (Eckerman 2002).

Study results could be pooled for only one comparison containing two studies. Otherwise pooling of results was not possible because of large variation in the types of interventions. Consequently we present results for individual studies. None of the included studies reported results for any of our secondary outcomes.

Interventions directed at organisations

Legislation and enforcement

We did not find any studies that had evaluated the effectiveness of occupational safety and health legislation and its enforcement in improving RPE use among employees.

Incentives (as in money or positive feedback)

We did not find any studies that had evaluated the effectiveness of incentives, when given to companies to improve RPE use among employees.

Information and guidance

We did not find any studies that had evaluated the effectiveness of information and guidance when given to companies to improve RPE use among employees.

Interventions directed at workers

We classified the results of the 14 included studies into four comparisons covering the only two available interventions: training and education. We present the effects of interventions for each comparison as follows.

1. Training versus no intervention

Primary outcome: Correct use of RPE

A CBA study in healthcare workers reported the pass rate for fit tests that indicated properly fitting respirators. This did not significantly increase in the workers who had received either training with a fit test (RR 1.17; 95% Confidence Interval (CI) 0.97 to 1.10) or training without a fit test (RR 1.16; 95% CI 0.95 to 1.42) compared to those who had no training (Hannum 1996) (Analysis 1.1).

One RCT showed non-significant differences in mean scores for respirator performance between groups (A, B, C) trained in performing fit checks and an untrained group (D) (Or 2012). The authors report only ANOVA test results for individual tasks and not group scores. The authors did not respond to our requests to provide us their raw data so that we could verify their results.

One RCT found fewer unsuccessful donnings and more consistent donnings for both common types of RPE used in the intervention group compared to the control group (Myers 1995). However, we could not extract the reported numerical figures from their publication due to the complicated way in which the authors had measured and reported RPE use.

2. Conventional training plus additions versus conventional training

Primary outcome: Use of RPE

One cluster-randomised trial found that there was no difference in the appropriate use of RPE after adjustment for the clustering effect (RR 1.41, 95% CI 0.96 to 2.07) (Carrico 2007) (Analysis

2.1). The clustering effect was 1.32 as presented in [Included studies](#) ('Design of the studies').

Primary outcome: Correct use of RPE as part of full-body PPE

One RCT compared computer-simulation training with conventional personal protective equipment (PPE) training ([Hung 2015](#)). The study found that participants in the computer-simulation training group performed significantly better in both donning and doffing full-body PPE than those in the conventional PPE training group (Mean Difference (MD) 0.52, 95% CI 0.14 to 0.90; and MD 1.16, 95% CI 0.70 to 1.62, respectively; [Analysis 2.2](#)).

Knowledge of correct use of RPE as proxy of actual correct use

One RCT compared interactive training with passive training and with an information screen and an information book ([Eckerman 2002](#)). The mean RPE performance score for the Programmed Instruction (PI-active) group, who received interactive training, was not different from that of the PI-passive group (MD 2.10, 95% CI -0.76 to 4.96). However, the PI-active group scored significantly higher than the INFO-book group (MD 4.20, 95% CI 0.89 to 7.51) and the INFO-screen group (MD 7.00, 95% CI 4.06 to 9.94). On the other hand, the PI-passive group's score was not different from that of the INFO-book group (MD 2.10, 95% CI -1.23 to 5.43) but it was higher than that of the INFO-screen group (MD 4.90, 95% CI 1.94 to 7.86) ([Analysis 2.3](#)).

3. Education versus no intervention

Primary outcome: Use of RPE

One RCT compared a multifaceted educational intervention to a no intervention control and reported the use of RPE from one to four years after the initiation of the intervention ([Donham 2011](#)). A small increase in RPE use was seen in the intervention group in the follow-up years. However, a statistically significant difference in RPE use between the two groups was only found at three-year follow-up (risk ratio (RR) 1.69, 95% CI 1.10 to 2.58). There was no considerable difference between intervention and control at one year follow-up (RR 1.30, 95% CI 0.97 to 1.76), at two years' follow-up (RR 1.33, 95% CI 0.96 to 1.83) or at four years' follow-up (RR 1.15, 95% CI 0.76 to 1.76; [Analysis 3.1](#)).

Three controlled before and after (CBA) studies compared education interventions to no intervention and presented self-reported RPE use at short term follow-up of six weeks ([Dressel 2007](#)) and at long term follow-up of six months ([Kim 2012](#)) and one year ([Gjerde 1991](#)). There were no significant differences in reported RPE use between the two groups either at short term follow-up (RR 1.07, 95% CI 0.91 to 1.26) or long term follow-up (pooled

RR 0.99, 95% CI 0.84 to 1.17; 206 farmers; 2 studies; [Analysis 3.2](#)).

One CBA by [Shamsi 2015](#) compared providing participants a free package containing a well-designed, light-weight helmet, a dust mask, safety gloves and a simple tailored pamphlet about the advantages of using PPE and the risks they can reduce with no intervention. There was no significant difference in the frequency of RPE use between the intervention and control groups (RR 2.05, 95% CI 0.74 to 5.69; [Analysis 3.3](#)).

One CBA by [Kim 2012](#) compared providing one evening of education on work-related asthma and agricultural causes; spirometry testing; respirator demonstrations and fit testing; exposure reduction strategies; and barriers to personal protective equipment (PPE) use with no intervention. There was no significant difference between intervention and control in the use of a respirator (PAPR) (RR 4.00, 95% CI 0.20 to 79.43; [Analysis 3.4](#)), or in conducting N95 respirator fit testing (RR 0.32, 95% CI 0.07 to 1.49; [Analysis 3.5](#)). However, participants in the intervention group were much more likely to use an N95 mask (RR 4.56, 95% CI 1.84 to 11.33; [Analysis 3.6](#)).

One RCT did not report sufficient data to be included in a meta-analysis but the authors reported a similar non-significant effect of the intervention on RPE use to the other studies, with an effect size of 0.05 and an F value of 0.43 (df = 143) ([Parkinson 1989](#)).

Primary outcome: Correct use of RPE as part of full-body PPE

One RCT compared a multifaceted educational intervention with a no intervention control and reported the use of RPE as part of full-body PPE ([Perry 2003](#)). The authors found no significant difference between the intervention and control groups in PPE use six months after the intervention (odds ratio (OR) 1.10, 95% CI 0.80 to 1.51). However, the authors did not report the figures on which their results are based. The authors also did not respond to our requests to provide us their raw data so that we could verify their results.

4. Motivational interview-based education versus traditional lectures

Primary outcome: Correct use of RPE as part of full-body PPE

One CBA compared motivational interviewing-based education and traditional lectures ([Navidian 2015](#)). The authors found that participants who underwent motivational group interviewing-based safety education scored higher on a checklist measuring PPE use (MD 2.95, 95% CI 1.93 to 3.97) than control workers who underwent traditional educational sessions ([Analysis 4.1](#)).

Quality of the evidence

We judged all studies to have a high risk of bias and therefore we downgraded the quality of the evidence by one level for all comparisons. All but one comparison had only a single study and therefore we did not downgrade the quality of the evidence for inconsistency nor publication bias for these comparisons. None of the comparisons had more than 400 participants and all but one study had a wide confidence interval including 1, and therefore the possibility of a considerable harmful or beneficial effect.

Therefore we downgraded the quality of the evidence by one level for all comparisons due to imprecision. We considered four studies to yield indirect evidence, which would have been sufficient reason to downgrade the level of evidence with one level in two comparisons because of indirectness. But there was no need for this as we had already downgraded the quality of evidence in both of these comparisons to very low.

For the controlled before and after studies, we found no reason to upgrade the quality of the evidence.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Conventional training plus fit test versus conventional training						
Patient or population: Health workers Settings: Healthcare institutes Intervention: Conventional training plus additions Control: Conventional training						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Conventional training	Conventional training plus additions				
Observed appropriate RPE use	531 per 1000	749 per 1000 (510 to 1000)	RR 1.41 (0.96 to 2.07)	64 (1 study)	⊕○○○ very low ¹	One cluster-RCT
Correct use of RPE as part of full-body PPE - Donning	The mean correct use of RPE as part of full-body PPE - donning in the control groups was 14.56 score	The mean correct use of RPE as part of full-body PPE - donning in the intervention groups was 0.52 higher (0.14 to 0.9 higher)		50 (1 study)	⊕○○○ very low ²	One RCT
Correct use of RPE as part of full-body PPE - Doffing	The mean correct use of RPE as part of full-body PPE - doffing in the control groups was 18.32 score	The mean correct use of RPE as part of full-body PPE - doffing in the intervention groups was 1.16 higher (0.7 to 1.62 higher)		50 (1 study)	⊕○○○ very low ²	One RCT

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ We downgraded the quality of evidence from high quality with one level because of very small sample size, with one level due to study limitations (unclear risk of bias for sequence generation and allocation concealment) and with one more level due to imprecision (a wide confidence interval for the RR).

² We downgraded the quality of evidence from high quality with one level because of very small sample size, with one level due to study limitations (unclear risk of bias for sequence generation, allocation concealment and detection bias) and with one more level due to indirect outcome (RPE measured as a part of PPE).

Education versus no intervention						
Patient or population: Workers Settings: Developed and developing countries Intervention: Education Control: No intervention						
Outcomes [#]	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No intervention	Education				
Use of RPE most of the time - 3 years after intervention	282 per 1000	476 per 1000 (310 to 727)	RR 1.69 (1.1 to 2.58)	170 (1 study)	⊕⊕○○ low ¹	One RCT
Reported RPE use among farmers - Short term follow-up (6 weeks)	875 per 1000	936 per 1000 (796 to 1000)	RR 1.07 (0.91 to 1.26)	105 (1 study)	⊕○○○ very low ²	One CBA
Reported RPE use among farmers - Long term follow up (6 months - 1 year)	734 per 1000	727 per 1000 (617 to 859)	RR 0.99 (0.84 to 1.17)	206 (2 studies)	⊕○○○ very low ³	Two CBAs
Use of safety mask while working	190 per 1000	390 per 1000 (141 to 1000)	RR 2.05 (0.74 to 5.69)	44 (1 study)	⊕○○○ very low ⁴	One CBA
Fit tested for N95	217 per 1000	70 per 1000 (15 to 324)	RR 0.32 (0.07 to 1.49)	52 (1 study)	⊕○○○ very low ³	One CBA
Use of N95 mask	174 per 1000	793 per 1000 (320 to 1000)	RR 4.56 (1.84 to 11.33)	52 (1 study)	⊕○○○ very low ³	One CBA

For each study, when more RPE use outcomes were reported, we selected the RPE use outcome with the most reliable information; two studies (Parkinson 1989, Perry 2003) did not report enough information to be included.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ We downgraded the quality of evidence from high quality with one level because of study limitations (unclear risk of bias for sequence generation and allocation concealment, and high risk of bias for attrition bias) and with one level due to imprecision (a wide confidence interval for the RR).

² Starting at low quality, we downgraded the quality of evidence to very low level because of study limitations (CBA study; high risk of bias for sequence generation, allocation concealment and detection bias) and small sample size.

³ Starting at low quality, we downgraded the quality of evidence to very low level because of study limitations (CBA study; high risk of bias for sequence generation, allocation concealment and detection bias) and imprecision (a wide confidence interval for the RR).

⁴ Starting at low quality, we downgraded the quality of evidence to very low level because of study limitations (CBA study; high risk of bias for sequence generation, allocation concealment and detection bias) and very small sample size.

Motivational interview-based education versus traditional lectures						
Patient or population: Factory workers Settings: Iran Intervention: Motivational interview-based education Control: Traditional lectures						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Traditional lectures	Motivational inter-view-based education				
Use of RPE as part of full-body PPE (score on checklist)	The mean use of PPE in the control groups was 8.22	The mean use of PPE in the intervention groups was 2.95 points higher (1.93 to 3.97 higher)		70 (1 study)	⊕○○○ very low ¹	One CBA
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval;						
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.						

¹ Starting at low quality, we downgraded the quality of evidence with one level because of imprecision due to very small sample size and a wide confidence interval for the MD. We would have downgraded the quality of evidence with one more level due to study limitations (unclear risk of bias for sequence generation and allocation concealment) but we had already reached very low quality. We found no reason to upgrade the quality of evidence.

DISCUSSION

Summary of main results

We included in this Cochrane review 14 published studies involving 2052 participants. We also identified one ongoing study. The interventions in these included studies were only in the education and training category. We did not find any studies evaluating organisational interventions, or incentives (either monetary or positive feedback) or disincentives (either sanctions or negative feedback).

There is very low quality evidence provided by three RCTs and five CBA studies that behavioural interventions, namely education and training, do not have an effect on the frequency or correctness of RPE use in workers. There is low quality evidence provided by one RCT that an educational intervention increased the use of RPE at three years' follow-up when compared to no intervention. However, in the same study there was no difference between intervention and control at one year's, two years' or four years' follow-up. There is very low quality evidence from one RCT that training leads to fewer unsuccessful donnings and more consistent donnings but we could not verify this because of unclearly reported results. There is also inconsistent very low quality evidence provided by two RCTs and one CBA study about the effect of education and training interventions on the use of respiratory protective equipment (RPE) as part of full-body personal protective equipment. Finally, there is very low quality evidence from one RCT that interactive training can improve knowledge of the correct use of RPE.

Overall completeness and applicability of evidence

Included studies had evaluated different types of RPE and results were mainly from self-reported assessment. It is apparent from the studies included in our Cochrane review that the provision of advice does not help in the use of RPE. The included studies also lacked significant information on the degree to which barriers to the use RPE while working could affect the results (e.g. types of RPE used at work or the attitude of workers when using RPE). This limits the usefulness and applicability of the results.

Moreover, most studies were conducted in developed countries, mainly in the USA, Canada and Germany. There were also different target populations, including healthcare, farm, production line and coke oven workers. Thereby readers should exercise caution when applying these findings to low- and middle-income countries, as well as other occupational sectors.

Quality of the evidence

We graded the quality of the evidence according to the GRADE system (GRADEpro 2008). We judged the evidence in one comparison as provided by one RCT to be low quality. We judged the quality of evidence provided by all the remaining 13 studies in all four comparisons to be very low. We downgraded the quality of evidence from high quality with one level because of study limitations and with another level due to imprecision of the estimate of intervention effect. We did not consider inconsistency or publication bias because there was only a single study included in all but one comparison. Six of the 14 included studies (43 %) used a controlled before and after study design. We found no reason to upgrade the quality of evidence provided by these controlled before-after studies. All studies failed to control for selection bias or demonstrate that they had done so by, for example, rigorous allocation concealment. Seven studies included fewer than 100 participants, which is in our opinion insufficient given the small effects found in the studies.

Potential biases in the review process

Our primary outcome measure was use of RPE. However, this was measured in various ways as there is no standard instrument to measure RPE use. In some studies there was already a quite high level of RPE use to begin with and it was therefore more difficult to increase. However, we could not take this into account in our analyses. It is also difficult to predict in which direction this would have biased our results. It could have either decreased or increased the effects of the interventions.

We obtained all relevant studies that we identified from the search. We independently screened these potential studies, assessed risk of bias and extracted data from included studies, and we resolved disagreements by discussion. We were also able to successfully contact the authors of two included studies to clarify the reported RPE use (Dressel 2007; Perry 2003). Therefore, potential bias due to the review process should be minimal.

Agreements and disagreements with other studies or reviews

The findings of this review are similar to those of a systematic review that aimed to evaluate the effectiveness and processes of occupational-based behavioural interventions for workers exposed to dermal and respiratory hazards (Lunt 2011). They found that worker-focused behavioural interventions had a limited, albeit positive, impact upon exposure. This review assessed not only RPE use but also a broader range of behavioural indicators. However, this review did not include eight further studies that are included in our review (Carrico 2007; Donham 2011; Eckerman 2002; Gjerde 1991; Hannum 1996; Kim 2012; Myers 1995; Or 2012).

AUTHORS' CONCLUSIONS

Implications for practice

According to the evidence provided by this Cochrane review, behavioural interventions - namely education and training - do not have a considerable effect on the frequency or correctness of RPE use in workers. This may be due to a lack of studies with a low risk of bias. Interventions to promote the correct use of RPE need to be better evaluated to provide evidence for their effectiveness before any strong recommendations can be made. There were no studies on incentives.

Implications for research

There is a lack of studies with a low risk of bias that evaluate the effectiveness of behavioural interventions to promote RPE use. The interventions used in the studies included in this Cochrane review focus primarily on education and training. We need studies evaluating the effectiveness of other interventions and combinations of interventions to improve RPE use in workers compared with education only. Examples of these other interventions include: legislation and enforcement; incentives (e.g. monetary or positive feedback); sanctions and negative feedback; and changes in the organisational safety climate or culture.

Given the small effects reported in studies included in this Cochrane review, the sample size of new studies should be at least 400 participants. This sample size is based on an estimate of a small effect size of 0.2 (Norman 2012). New studies should use and clearly report randomised sequence generation, allocation

concealment and assessor blinding. New studies should evaluate the effectiveness of behavioural interventions for improving the use of RPE at both an organisational and individual level using different types of workers. Studies should be conducted in both high-income as well as low- and middle-income country settings. Behavioural interventions targeted at the worker level should be carried out in small-scale industries in low- and middle-income countries, while those targeted at the national or organisational level should be conducted in larger organisations in high-income countries. Future studies should also consider and take into account the impact of known barriers to RPE use, such as perception of health risk, employers' attitude, and ease and comfort of use.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Carrico 2007

Methods	Cluster-randomised controlled trial 20 participants were randomly assigned to either an intervention (n = 10) or control group (n = 10). The outcome was measured in 42 patients each for the intervention and control group. Clustering of nurses was not taken into account
Participants	Setting: a university hospital in the USA Registered nurses who were employed by the hospital; mobile or per diem nurses were excluded Recruitment: 20 participants were randomly assigned to an intervention or control group
Interventions	Intervention: classroom training plus bio-simulated visual training. The bio-simulator consisted of a patient dummy that could visualise with fluorescent powder how coughing disperses particles in the air Control: only classroom training
Outcomes	1. Appropriate RPE use during patient care, as observed by 2 trained blinded observers. Observers noted if, in patients exhibiting respiratory symptoms, PPE items were used. This could be either that the nurse placed a mask on the patient or used a mask themselves. Both were considered valid protection techniques. Assessments were made in the weeks immediately following training This outcome was measured in 42 patients in the intervention and control group 2. Pre-and post teaching knowledge of respiratory pathogen transmission
Notes	Patient bio-simulator (Medical Education Technologies, Inc. (METI), Sarasota, FL)

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The details of random sequence generation were not reported
Allocation concealment (selection bias)	Unclear risk	This information was not provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trained observers were blinded to the participants' group assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were observed and the main outcomes of appropriate RPE use during patient care was recorded

Carrico 2007 (Continued)

Selective reporting (reporting bias)	Low risk	Results of the 2 important outcomes mentioned, frequency of self-RPE use and use of RPE on patients, were presented
Similarity of baseline characteristics	Low risk	Balanced baseline characteristics between the 2 groups were reported

Donham 2011

Methods	Randomise controlled trial in 308 farms randomly recruited from farms in a 9-county area in Northwest Iowa between 1998 and 2003. The farms were stratified based on similarities of farm size, type of commodity production and frequency of self-reported farm injuries. They were paired within the strata, then randomly assigned to either Certified Safe Farm (CSF) or control group. Per farm the principal operator of the farm was the study unit	
Participants	Setting: 9-county area in Northwest Iowa, USA Recruitment: 308 farms (150 CSF intervention farms and 158 control farms) Principal operators of the farms, such as the primary owner or manager, were the study units Baseline characteristics of the farms and the principal operators of 2 groups were similar The exception was operator's education of which 39% of the CSF intervention group had bachelors degrees or higher compared to 27% in the control group	
Interventions	Intervention: educational intervention. The CSF intervention was a multifaceted intervention consisting of 4 elements: 1. clinical occupational and wellness screening with fit testing of RPEs, 2. educational support: newsletters, website and meetings, 3. on-farm safety audits with set safety standard and 4. a performance incentive with a UDS200 payment for achieving at least 85% of the audit score Control: no intervention	
Outcomes	1. Use of respirator assessed by questionnaire: "What percentage of the time did you use respiratory protection when working among grain dust?". Answers of more than 75% were scored as 'use of RPE' and less than 75% as 'no use of RPE'. The outcome was assessed at baseline and yearly until 4 years after the intervention 2. Occupational respiratory symptoms including airways symptoms and symptoms of organic dust toxic syndrome. Symptoms were self-reported using an assessment tool designed for farm organic dust exposure, as developed by Rylander and co-workers At baseline there were 141 intervention farms that responded and 140 control farms, at year 1 the figures were 129 and 126, at year 2 this was 120 and 108, at year 3 this was 99 and 71 and at year 4 this was 75 and 55, respectively	
Notes	-	

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement

Donham 2011 (Continued)

Random sequence generation (selection bias)	Unclear risk	Reported that “These farms were then paired within strata of the variables mentioned above and randomly assigned to either the intervention or control group (CSF intervention, n =150 and controls, n =158)”. No information on random sequence generation was presented
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment was provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trained interviewers who assessed occupational respiratory symptoms were blinded to the interventions
Incomplete outcome data (attrition bias) All outcomes	High risk	308 farms (150 CSF intervention farm and 158 controls) were recruited, but 281 farms (91.2%), 141 CSF intervention farms and 140 controls, were analysed for respirator use and respiratory symptoms at entry Farms dropped out from the study every year (Table 3 in the paper). At the 4th year of follow-up results were reported from only 75 farms (50.0%) in the CSF intervention group and 55 farms (34.8%) in the control group
Selective reporting (reporting bias)	Low risk	Results of the 2 important outcomes mentioned, respirator use and respiratory symptoms, were presented
Similarity of baseline characteristics	Low risk	The results show that the demographics and exposure characteristics of the CSF intervention and control groups were comparable

Dressel 2007

Methods	Controlled before and after study
Participants	Setting: Bavaria, Germany Recruitment: 105 out of 120 eligible farmers with occupational asthma mainly sensitised against cow dander and storage mites took part in a 1-day educational programme organised by 2 German statutory accident insurance institutions for the agricultural sector A total of 81 participants (49 males (mean $\pm$ SD age 49.8 $\pm$ 9.1 years) and 32 females (45.9 $\pm$ 8.6 years)) were included in the intervention group as they were regularly working at a stable and were able to return to the same location for a second visit 4 to 6 weeks

	after the intervention The control group comprised farmers with occupational asthma not participating in the educational programme (19 males (44.5 ± 10.9 years) and 5 females (41.2 ± 7.7 years)). They were visited at their farms for baseline measurement and again 4 to 6 weeks later
Interventions	Intervention: 1-day educational programme. “The education, of 4-5 h duration, included two presentations by one of the authors of the present article (J. Sultz), who is a pulmonologist and occupational physician. The first presentation provided general information about the pathogenesis of asthma and allergies, environmental influences, medication and prevention. The second presentation gave details about major occupational allergens causing asthma, particularly cow dander and mites, with special focus on prevention in the workplace based on original data. All major issues were illustrated by examples drawn from the patients’ cases. A representative of the insurance institution added further information about technical and organisational means of allergen avoidance and demonstrated the use of personal protective equipment.” (page 546) Control: no intervention
Outcomes	Wearing headgear during stable work measured at baseline and at 4 to 6 weeks follow-up
Notes	Authors confirmed that the headgear in question meant some form of respirator mask; information requested by email to D Nowak on 23 October 2014

*Risk of bias**Risk of bias*

Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	High risk	There was no allocation of participants into study groups: the intervention group consists of an opportunity sample of farmers participating in an educational programme, whereas control group participants were sampled from those that did not participate
Allocation concealment (selection bias)	High risk	There was no allocation into groups
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessment of behaviours was done by the participants themselves and thereby introduced a possible bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The authors do not give any indication as to whether they followed up all study participants or if some were lost to follow-up
Selective reporting (reporting bias)	Low risk	All measured outcomes appear to have been reported

Dressel 2007 (Continued)

Similarity of baseline characteristics	High risk	Intervention group participants were significantly more often (73% versus 42%) currently experiencing one or more of the following respiratory symptoms at work: shortness of breath, cough with or without phlegm, wheeze or nasal irritation. Use of headgear was similar in both groups (76.5% versus 79.2%)

Eckerman 2002

Methods	Randomised controlled trial	
Participants	Setting: Oregon Health Science University, USA Recruitment: 123 adults were recruited through advertisements in local newspapers, the website of Oregon Health and Science University, and flyers distributed at a liberal arts university	
Interventions	4 intervention groups: 1. Programmed instruction (PI) active (n = 32) 2. PI passive (n = 31), 3. INFO-book (read book, non-interactive) (n = 20) 4. INFO-screen (read screen, non-interactive) (n = 32) The intervention provided basic respiratory protection information, addressing the following: uses (preventing symptoms), limitations (immediately dangerous to life or health conditions, seal, fit tests), and maintenance of air-purifying and supplied air respirators (SAR; valve, cartridge replacement); recognition of respiratory hazards (lead, solvents, carbon monoxide; acute and chronic effects); selection of proper respirators for different hazards (material safety data sheets (MSDS), product labels, permissible exposure limits) and measurement of hazard levels	
Outcomes	Performance scores for basic respiratory protection information measured by quiz test contained four-item multiple-choice questions done on the computer screen This outcome was assessed before and immediately, 1 week and 2 months after the intervention	
Notes	-	

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Participants were randomly assigned to conditions when they arrived." (page 315) However, there was no information on how randomisation was conducted
Allocation concealment (selection bias)	Unclear risk	No information provided

Eckerman 2002 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	High risk	At 2 months: 36 % (44/123) loss to follow-up, in which: 13/32 dropped out from PI active, 11/32 dropped out from PI passive, 8/28 dropped out from INFO-book and 12/32 dropped out from INFO-screen
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported
Similarity of baseline characteristics	Unclear risk	No information provided

Gjerde 1991

Methods	Controlled before and after study
Participants	Setting: 108 (89%) of 121 farms producing pork that qualified from 7 counties in eastern Iowa, USA. Every farm contributed on average 2 workers; 88% were men; there were no differences in age, education or years in farming between the intervention and control group Recruitment: 102 swine confinement workers from 7 southeastern counties in Iowa were designated as the intervention group and 107 swine confinement workers from 7 northeastern counties in Iowa as the control group
Interventions	Intervention: educational intervention consisting of a series of 6 educational home study modules, a project logo and an evening session in which respirator use and gas measurement were demonstrated. Of the intervention group 49 workers (48%) attended the evening session Control: no intervention
Outcomes	Self-reported improvements of knowledge, attitudes and behaviours, of which one was dust mask use, at baseline and 1 year after intervention
Notes	-

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Study was not randomised
Allocation concealment (selection bias)	High risk	There was no allocation concealment

Gjerde 1991 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessment was done using a 13-item self-reported behaviours questionnaire in the study participants and thereby introduced a possible bias
Incomplete outcome data (attrition bias) All outcomes	High risk	In the intervention group (n = 102), 77 (75%) and 68 (67%) of participants provided useful information at baseline (T1) and 1 year after intervention (T2), respectively In the control group (n = 107), 95 (88%) and 86 (80%) participants provided useful information at T1 and T2, respectively Data appropriate for the chosen analyses were obtained from 49 participants in the intervention group and 79 participants in the non-intervention group
Selective reporting (reporting bias)	Low risk	All items in the assessment questionnaire were analysed
Similarity of baseline characteristics	Low risk	An analysis of the demographics of the 2 groups showed no significant differences with respect to age, education, years in farming or type of farming

Hannum 1996

Methods	Controlled before and after study
Participants	Setting: Veterans Affairs hospital, Virginia, USA Recruitment: 179 hospital employers in a 775-bed Veterans Affairs hospital
Interventions	Intervention: employees in Group A received one-on-one training by the hospital's industrial hygienist and were fit tested as part of this training using irritant smoke to test if the RPE fitted (N = 52) Employees in Group B received classroom instruction and demonstration by infection control nurses in the proper use of respirators, but were not fit tested as part of training (N = 64) Control: employees in Group C received no formal training (N = 63)
Outcomes	1. Correct fit of RPE: if there was coughing or detection of smoke during a qualitative fit test using irritant smoke the RPE was considered not to be adjusted correctly 2. Direct cost of each method of training 3. Cost of employee-hours lost during training
Notes	-

Risk of bias

Risk of bias

Hannum 1996 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not a randomised study. The project started with participants being taught by the industrial hygienist (Group A). Later a group was taught by nurses (Group B) as the progress of individual training was slow. Additionally there was a group of those who had not received training (Group C)
Allocation concealment (selection bias)	High risk	There was no allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The assessors of qualitative fit testing were blinded to the group (i.e. A, B or C) of the participant tested
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 179 recruited healthcare workers provided data for the results that were analysed for qualitative fit test in respirator use
Selective reporting (reporting bias)	Low risk	Results of the 3 outcomes, qualitative fit test using, direct cost of each method of training and cost of employee-hours lost during training, were reported
Similarity of baseline characteristics	Unclear risk	No information available

Hung 2015

Methods	Randomised controlled trial
Participants	Setting: Hong Kong Recruitment: 50 healthcare workers (registered nurses, enrolled nurses, healthcare assistants) in the 24-hour outpatient department of a private hospital; able to read English, with basic computer operation skills
Interventions	Intervention (n = 25): received conventional personal PPE training plus computer-simulated training using the proposed simulation program - web-based interactive software with a user-friendly graphical interface for users to practise the use of PPE via dragging and dropping various PPE onto a virtual healthcare worker and by responding to multiple choice questions online Control group (n = 25): received conventional PPE training
Outcomes	1. Performance in PPE donning and doffing, measured as scores for PPE use that included a N95 respirator, face-shield, cap, gown and gloves. The scores reflected overall skill in the use of PPE 2. Errors in simulated training and user satisfaction with the use of the computer program

Hung 2015 (Continued)

	(measured in the intervention group only) These outcomes were assessed 1 week after the training in the control group and after 2 weeks in the intervention group

Notes	

Risk of bias **Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote from the first paragraph of Research Design and Procedure (page 53): "The subjects were randomly assigned to the control and experimental group of the same size."
Allocation concealment (selection bias)	Unclear risk	Quote from the first paragraph of Research Design and Procedure (page 53): "the subjects were randomly assigned to the control and experimental group of the same size."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated whether the reviewers were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No mention of attrition
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported
Similarity of baseline characteristics	Low risk	Comparable baseline characteristics are reported in Table 1 of the report

Kim 2012

Methods	Controlled before and after study
Participants	Setting: West Elgin Community Health Centre (WECHC), Canada Recruitment: 68 farmers were recruited via advertisements (local newspaper) and from previous surveys: 38 farmers attended the educational intervention and 30 farmers formed the control group
Interventions	Intervention: 1 evening educational programme at the WECHC, led by clinicians, safety consultants and suppliers of safety equipment. The programme consisted of rotating stations with information on work-related asthma and agricultural causes; spirometry testing; respirator demonstrations and fit testing; exposure reduction strategies; and barriers to personal protective equipment use Control group: no intervention

Outcomes	1. Occupational health and safety (OHS) knowledge 2. Use of PPE including reported mask use, use of N95 mask, fit testing for N95, use of respirator (powered air purifying respirator) and use of mask while brushing animals 3. Dust and mould reduction strategies including no dry sweeping of spills, wet sweeping of spills, high efficiency particulate air filter use, spraying feed or bedding, ensuring crops are dry before storing and anti-mould spray use 4. Engineering and procedural controls including ventilation in grain storage areas, ventilation in bar, non-manual feeding system, exhaust generators outdoors and separate work and home laundry These outcomes were assessed using a self-completed questionnaire before and 6 months after intervention
Notes	-

<i>Risk of bias</i>		<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not a randomised study
Allocation concealment (selection bias)	High risk	No allocation concealment Quote: "Participants who were able to attend the educational evening formed the intervention group; those unable to attend formed the control group. This pilot study was not randomized."
Blinding of outcome assessment (detection bias) All outcomes	High risk	The self-completed questionnaire introduced a possible bias
Incomplete outcome data (attrition bias) All outcomes	High risk	76% (29/38) of the intervention group and 77% of the control group completed the follow-up survey 6 months after intervention
Selective reporting (reporting bias)	Low risk	Results of all expected outcomes were reported
Similarity of baseline characteristics	High risk	Most baseline characteristics were comparable between the 2 groups, but differences in terms of sex, type of farm and respiratory symptoms were reported (Table 1, page 459 of the paper) Results of the 3ree outcomes, qualitative fit test using, direct cost of each method of training and cost of employee-hours lost during training, were reported

Myers 1995

Methods	Randomised controlled trial No information on study period
Participants	Setting: USA Recruitment: 64 white-collar workers with inexperience of RPE use Exclusion criteria: direct affiliation or business responsibility with the research, design or manufacture of RPE; previous training in the use of RPE; previous experience with wearing RPE in their jobs; facial hair that would compromise the seal of RPE
Interventions	Intervention (n = 32): training to don the RPE using the +/- fit check as an aid Control (n = 32): training to don the RPE without conducting a +/- fit check The training period was 2 days
Outcomes	Successful RPE donning tested over 3 days immediately after training but the information was unclear how the authors measures successful RPE donning
Notes	

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information available. Quote: "Subjects were randomly divided into three groups."
Allocation concealment (selection bias)	Unclear risk	No information available. Quote: "Subjects were randomly divided into three groups."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear information
Selective reporting (reporting bias)	Unclear risk	Unclear outcome reported
Similarity of baseline characteristics	Unclear risk	No information provided

Navidian 2015

Methods	Controlled before and after study January to August 2014
Participants	Setting: Hamedan, Iran Recruitment: 70 production line workers at glass production facilities Exclusion criteria: participation in safety education classes during the last year, having a history of occupational injury or trauma, the presence of disease or other physical

	limitation, illiteracy and absence from more than one educational session
Interventions	Intervention (n = 35): 4 educational sessions based on motivational interviewing, which were conducted in 4 groups of 8 to 10 participants Control group (n = 35): participants attended 4 x 1-hour safety education sessions that were conducted as traditional lectures
Outcomes	Safety awareness, attitude and performance in the use of PPE which included respirators but the specific data of RPE use was not reported These outcomes were assessed before and 12 weeks after the intervention
Notes	-

*Risk of bias**Risk of bias*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote from the first paragraph of Methods on page 3: "Based on the sample volume formula with $\alpha = 5\%$ and test power of 90 %, 35 subjects were randomly assigned to the intervention group and 35 to the control group."
Allocation concealment (selection bias)	Unclear risk	Quote from the first paragraph of Methods on page 3: "Based on the sample volume formula with $\alpha = 5\%$ and test power of 90 %, 35 subjects were randomly assigned to the intervention group and 35 to the control group."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned in the paper
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned in the paper
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Similarity of baseline characteristics	Low risk	The baseline characteristics were comparable

Or 2012

Methods	Randomised controlled trial
Participants	Setting: department of nursing and health sciences, Hong Kong, China Recruitment: 84 first-year undergraduate nursing students with previous inexperience in respirator fit testing or fit checking. They were randomly divided into 4 intervention groups. Each group included 21 students
Interventions	Group A: conventional quantitative PortaCount fit test with fit check training Group B: no conventional PortaCount fit test with fit check training Group C: conventional PortaCount fit test without fit check training Group D: no conventional PortaCount fit test without fit check training
Outcomes	Respirator fitness. The measurements were conducted continuously for 15 minutes, with particle concentration measurements averaged over 1 minute
Notes	-

<i>Risk of bias</i>		<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The participants were divided randomly into four groups..." (page 512) No information on how randomisation was actually done
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information available about who assessed the respirator fitness
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided
Selective reporting (reporting bias)	High risk	Expected outcomes were not presented clearly
Similarity of baseline characteristics	Low risk	Baseline characteristics were similar among groups. Quote: "One-way ANOVA compared the means of participants' ages, heights, and weights in the four groups; no statistically significant differences were found. Chi-square tests were used to analyze the other demographic variables; no significant differences were found. No significant differences of fit factors while performing nursing procedures were found among the four groups." (page 513)

Methods	Cluster-randomised controlled trial
Participants	Setting: USA and Canada Recruitment: 14 coke plants, or 7 pairs (6 American; 1 Canadian), matched regarding geographic location, work force size and ethnic composition, were chosen from the population of 28 operating coke oven facilities in the USA and Canada in 1984. In each pair one would be randomly assigned to receive the education programme and the other would serve as the control plant. From the intervention cluster 209 workers were randomly chosen for the intervention and likewise 119 workers from the control cluster
Interventions	Intervention: education programme. "The educational program was composed of four core modules. The first module provided an overview of the history of the USWA's activities in improving the safety and health conditions of coke oven plants. The second module provided information about the types of cancer associated with coke plant work and the components of an effective medical surveillance program. The third module delineated the provisions of the OSHA Coke Oven Standard. In this module, information on personal workplace practices (eg, using respirators, engaging in hygienic behavior, refraining from eating or drinking in regulated areas, etc) as well as proper engineering controls was discussed. Finally, the fourth module described the current status of the control program at each plant." "The educational program was delivered on four occasions during a 2-year period at each of seven coke oven plants. Although the core program, which was formally evaluated, remained constant, the programs were also augmented to meet specific requests and/or needs of individual plants. Thus, additional information was presented on such topics as techniques for diagnosing lung cancer, workers' compensation, types of respirators, and results of government actions (OSHA and/or Environmental Protection Agency inspections) which had taken place at the plant." (page 465) Control: no intervention
Outcomes	1. Knowledge of the coke oven standard 2. Knowledge of cancer hazards 3. Personal workplace practice (wash face/wash hands before lunch, shower at plant, eat or drink anything other than water on battery, smokers who smoke last year, had physical in last year, wear face shield/safety glasses/goggles, wear respiratory) They were assessed before and 1 month and 6 months after each intervention programme
Notes	Results for interventions are presented only as repeated measures ANOVA results

Risk of bias**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "From the population of 28 operating coke oven facilities in the United States and Canada in 1984, we sought to select pairs of plants in which one (the "experimental" plant) would be randomly assigned to receive the education program and the other would serve as

Parkinson 1989 (Continued)

		the control plant.” (page 466) The authors do not give any details on how they performed the randomisation
Allocation concealment (selection bias)	Unclear risk	The authors do not give any details about allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Given the nature of the intervention, it was not possible to blind the participants or the intervention providers. However, the telephone interviewers obtaining follow-up data could have been blinded but the authors do not report whether this was done
Incomplete outcome data (attrition bias) All outcomes	High risk	The authors do not report what happened to participants lost to follow-up
Selective reporting (reporting bias)	High risk	The authors do not report all the same data at follow-up as at baseline
Similarity of baseline characteristics	Unclear risk	Quote: “The one issue on which the groups differed was their baseline level of job-related health concerns. As Table 2 shows, participants were more likely to acknowledge such concerns than were non-participants, that is, workers from the same plants who did not attend the program.” (page 468)

Perry 2003

Methods	Randomised controlled trial
Participants	Setting: 400 dairy farmers certified to apply pesticides to field crops, Wisconsin, USA Recruitment: 100 participants were allocated to the intervention group and 300 were in the control group A total of 385 participants completed the follow-up interview
Interventions	Intervention: educational intervention (3 hours of education sessions) 3-hour educational sessions were conducted with approximately 100 randomly assigned participants. Sessions targeted 4 educational messages: (1) existing evidence of excess cancers among farmers; (2) simulation of pesticide exposure presented through a slide show and description; (3) feedback of self-reported data collected from the farmers, reporting on frequency of exposure and gear use; and (4) cognitive behavioural strategies that can be adopted to reduce pesticide hazards Control: attended the standard re-certification meeting

Perry 2003 (Continued)

Outcomes	1. Use of protective gear (use of any gear other than gloves during the most recent application) 2. Full PPE compliance, including the self-reported use of PPE including a respirator. However, the specific information on use of the respirator could not be extracted from the PPE compliance outcome 3. Self-reported dermal exposure during the most recent application 4. Decreased number of pesticides applied These outcomes were assessed 6 months after intervention
Notes	-

<i>Risk of bias</i>		<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomisation method was used to allocate participants to each intervention group
Allocation concealment (selection bias)	Unclear risk	This information was not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded participants and outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Each participant was interviewed over the telephone on 2 occasions after their first pesticide application of the season and attended a winter pesticide re-certification meeting. The loss to follow-up was 6 out of 100 farmers in the intervention group and 9 out of 300 farmers in the control group
Selective reporting (reporting bias)	Low risk	All items in the questionnaire were reported
Similarity of baseline characteristics	Low risk	Baseline demographic and pesticide application practices in the 2 treatment groups were not different between the groups

Shamsi 2015

Methods	Controlled before and after study
Participants	Setting: Isfahan, Iran Participants: 44 workers constructing 2 subway stations in Isfahan. Workers in random subway stations under construction from the north region formed the intervention group and workers in random subway stations under construction from the central region of Isfahan were the control group. They were far away from each other and had no relationship

Interventions	Intervention (n = 23): received a free package containing a safety helmet with a tailored message affixed to it, a dust mask and safety gloves and an educational pamphlet. This was a 4-week intervention Control group (n = 21): received no training
Outcomes	Use of PPE including the use of helmet, safety mask, safety gloves and safety shoes while working. Using a safety mask while working was considered to be RPE use These outcomes were measured before and after 6 weeks
Notes	-

<i>Risk of bias</i>		<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not done
Allocation concealment (selection bias)	High risk	Not done
Blinding of outcome assessment (detection bias) All outcomes	High risk	Self-reported behaviours
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not reported
Selective reporting (reporting bias)	Low risk	All expected outcomes were presented
Similarity of baseline characteristics	Low risk	The 2 groups had no significant differences in demographic variables such as age, daily work hours, literacy level and work history

CSF: Certified Safe Farm

PI: programmed instruction

PPE: personal protective equipment

RPE: respiratory protective equipment

SD: standard deviation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adewoye 2014	This study aimed to assess the effect of a health education intervention on awareness and practices of occupational safety among electric arc welders. It is not related to our review objective
Bailey 2010	The intervention in this study emphasised both skin and respiratory protection measures The outcome that was measured was the incidence of sensitisation, which was not one of our inclusion criteria
Becker 2004	The study was only a survey comparing worker activities before and after a training programme
Casalino 2015	This study aimed to compare two different strategies for training students in the proficient use of personal protective equipment (PPE) and to evaluate the frequency and number of errors occurring during donning and doffing of the PPE currently proposed for protecting healthcare workers against ebola virus disease. It is not related to our review objective of evaluating behavioural interventions for promoting respiratory protection use
Contreras 2012	This was a correlative study to evaluate PPE use after training and PPE distribution. Respirator use was part of the training. However, no comparative results were assessed in a control group
Crippa 2007	This study aimed to assess the efficacy of a specific educational programme in one group of hairdressing trainees, aged from 15 to 21 years, attending three technical schools, without a control group
Fu 2013	This was a before and after participatory training study in one group of welders from small and medium sized enterprises in China
Gershon 2009	This was an experimental pre-post intervention study in one group of emergency medical services workers in the USA
Harber 2013	This study did not aim to increase the use of RPE.
Harber 2014	This study did not aim to increase the use of RPE.
Huaroto 2013	This study had only one pre- and two post-intervention measurements from one group. Participants were healthcare workers exposed to biologic hazards, including tuberculosis. The type of intervention was information-training
Jenkins 2007	This was a non-randomised, non-controlled study. It had only one pre-post intervention group for assessing the improvement in PPE use in dairy farmers
Myong 2016	This was a before and after study with only two time points in one group of medical students
Woith 2015	This was a one-group experiment to assess the feasibility of a photovoice study on promoting respirator use in healthcare workers

PPE: personal protective equipment

RPE: respiratory protective equipment

Characteristics of ongoing studies [ordered by study ID]

Chen 2016

Trial name or title	Study protocol: a cluster randomized controlled trial to assess the effectiveness of a multi-pronged behavioural intervention to improve use of personal protective equipment among migrant workers exposed to organic solvents in small and medium-sized enterprises
Methods	This cluster RCT will be conducted in Baiyun district in Guangzhou, China
Participants	920 Migrant workers who do not have local registered permanent residence, are the first-line production workers exposed to organic solvents, working for more than 1 month in the 60 investigated enterprises
Interventions	Intervention arm 1 (n = 20 enterprises): A top-down intervention including: 1. Occupational health education towards managers and occupational health personnel in each enterprise will be accomplished in the first week of intervention by trained educators. It will focus on enterprises' responsibilities on occupational health; and benefits they will gain by creating a healthy workplace and improving workers' health; as well as activities they could take to achieve the goal, e.g. providing appropriate PPE and establishing and enforcing a supervision plan 2. General health education: One lecture on PPE utilization will be organised among migrant workers in the first week of intervention, delivered by two trained educators. The lecture will focus on the introduction of organic solvents, dangers of not using PPE, and how to properly select, use and store of PPE. Related brochures and posters will be delivered to migrant workers at baseline and 3-month follow-up of intervention 3. mHealth intervention: PPE utilization and other related occupational health messages will be sent twice a week through Instant Message Apps, including WeChat, Tencent QQ and Fetion, depending on which App is more commonly used by each migrant worker Intervention arm 2 (n = 20 enterprises): A comprehensive intervention, including: 1. The same intervention as that in the intervention arm 1; 2. Peer education will be organised once a month. Each peer group will include 8-15 migrant workers and one of them will be assigned as a group leader based on the voluntary principle. Group leaders will receive a course on peer education and a handbook designed by the research team (WC, XL and SF), as well as establish contact with our project coordinators (TL, FZ, SH and JS) to send feedback and get help timely. The overall 6 monthly peer educations will be launched by group leaders for no longer than 60 min each time. The intervention will begin with an ice-breaking game and introduction of peer education in the 1st month, followed by organic solvents and the related protection education in the 2nd month, how to use PPE and personal experiences of benefits and barriers of use PPE in the 3rd-5th months, and maintenance of PPE utilization in the 6th month. In addition, group leaders will be asked to monitor other group members' PPE utilization behaviour in the workplace. Every month, all group leaders will receive 50 RMB (8 \$USD) and the top five best performing leaders will receive additional 50 RMB as a token of appreciation Control arm (n = 20 enterprises): No intervention.
Outcomes	1. Self reported PPE use during the last week (i.e. organic respirator, dust mask or surgical mask) 2. Occupational health knowledge will be measured by 10 questions related to organic solvents and PPE utilization. Questions were designed by the researchers according to "The usage criterion of personal protective equipment against occupational diseases in organic solvents workplace". Correct answer for each question will achieve a score of 1, giving a total possible score of 10 3. Attitude towards PPE utilization. A scale of 9 items was developed by the researchers to assess migrant workers' attitude towards PPE utilization. The scale includes four dimensions, i.e. willingness to use, self-efficacy and perceived benefits and barriers. This measure will comprise 9 items and each will be rated on a 5-point Likert scale with 'strongly agree' scoring 5 and 'strongly disagree' scoring 1, giving an overall score ranging between 9 and 45

Chen 2016 (Continued)

	4. Participation in occupational health check-up will be measured by whether migrant workers have taken part in occupational health check-up during the past 6 months, and the number of occupational health check-ups migrant workers have received Data will be collected at baseline, 3-month follow-up and 6-month follow-up (the end of the intervention), respectively
Starting date	This trial will last 6 months.
Contact information	lingli@mail.sysu.edu.cn
Notes	

DATA AND ANALYSES

Comparison 1. Training versus no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Properly fitting RPE	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Healthcare workers fit tested at 6 months follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Healthcare workers not fit tested at 6 months follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Conventional training plus additions versus conventional training

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Observed appropriate RPE use	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Correct use of RPE as part of full-body PPE	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Donning	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Doffing	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Knowledge of RPE use at one-week follow-up	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 PI-active versus PI-passive	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 PI-active versus INFO-book	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 PI-active versus INFO-screen	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.4 PI-passive versus INFO-book	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.5 PI-passive versus INFO-screen	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 3. Education versus no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Use of RPE most of the time	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 1 year after intervention	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 2 years after intervention	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 3 years after intervention	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 4 years after intervention	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Reported RPE use among farmers	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Short term follow-up (6 weeks)	1	105	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.91, 1.26]
2.2 Long term follow up (6 months - 1 year)	2	206	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.84, 1.17]
3 Using safety mask while working	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4 Use of RPE (PAPR)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Fit tested for N95	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Use of N95 mask	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 4. Motivational interview-based education versus traditional lectures

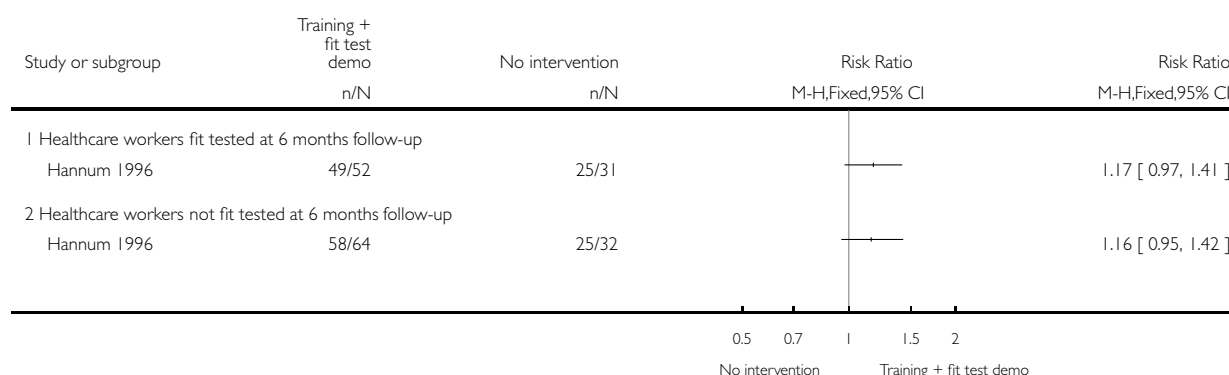
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Use of RPE as part of full-body PPE	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Training versus no intervention, Outcome 1 Properly fitting RPE.

Review: Behavioural interventions to promote workers' use of respiratory protective equipment

Comparison: 1 Training versus no intervention

Outcome: 1 Properly fitting RPE

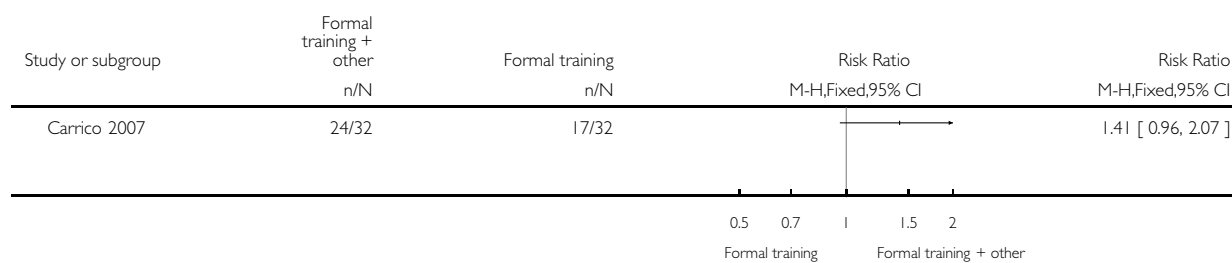


Analysis 2.1. Comparison 2 Conventional training plus additions versus conventional training, Outcome 1 Observed appropriate RPE use.

Review: Behavioural interventions to promote workers' use of respiratory protective equipment

Comparison: 2 Conventional training plus additions versus conventional training

Outcome: 1 Observed appropriate RPE use

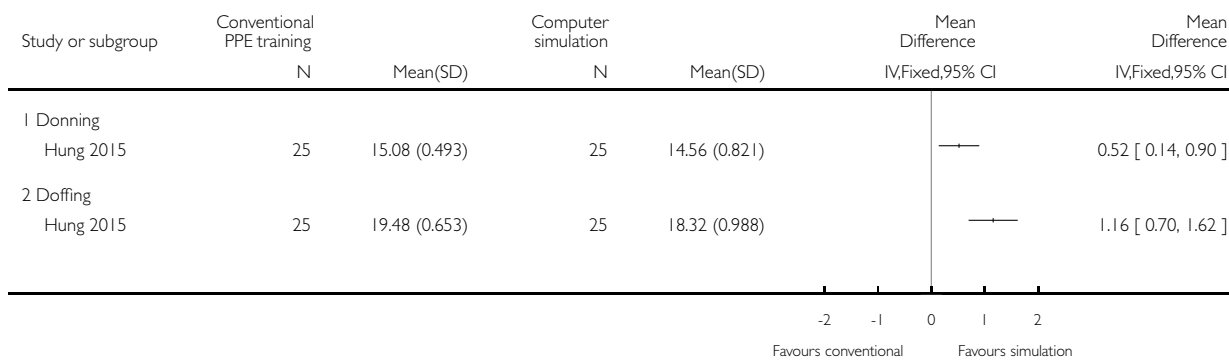


Analysis 2.2. Comparison 2 Conventional training plus additions versus conventional training, Outcome 2 Correct use of RPE as part of full-body PPE.

Review: Behavioural interventions to promote workers' use of respiratory protective equipment

Comparison: 2 Conventional training plus additions versus conventional training

Outcome: 2 Correct use of RPE as part of full-body PPE

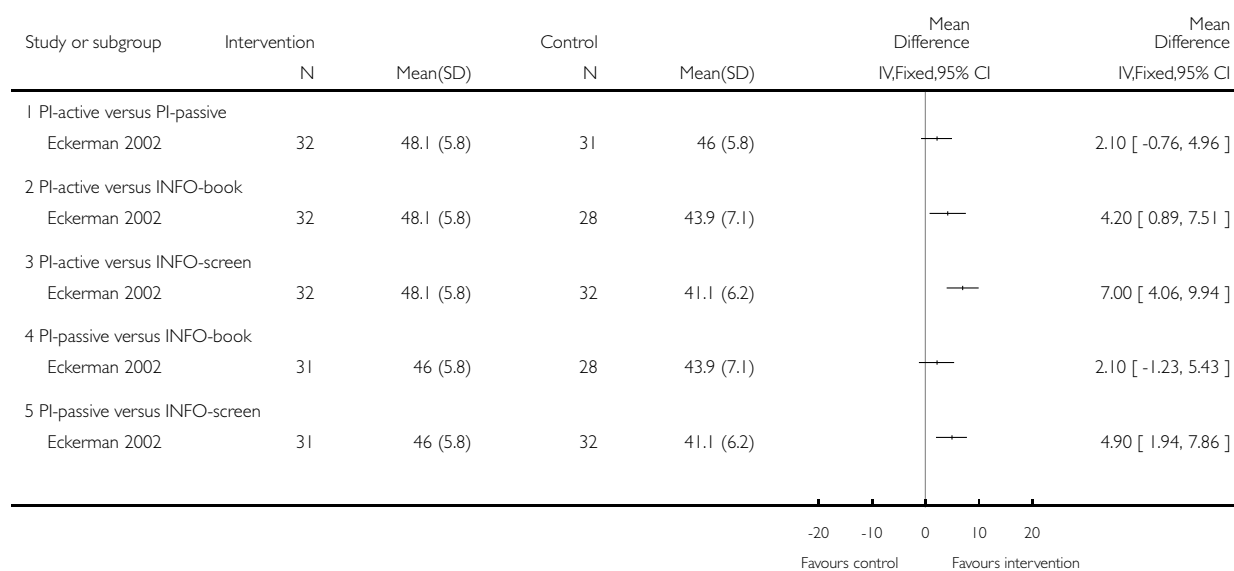


Analysis 2.3. Comparison 2 Conventional training plus additions versus conventional training, Outcome 3 Knowledge of RPE use at one-week follow-up.

Review: Behavioural interventions to promote workers' use of respiratory protective equipment

Comparison: 2 Conventional training plus additions versus conventional training

Outcome: 3 Knowledge of RPE use at one-week follow-up

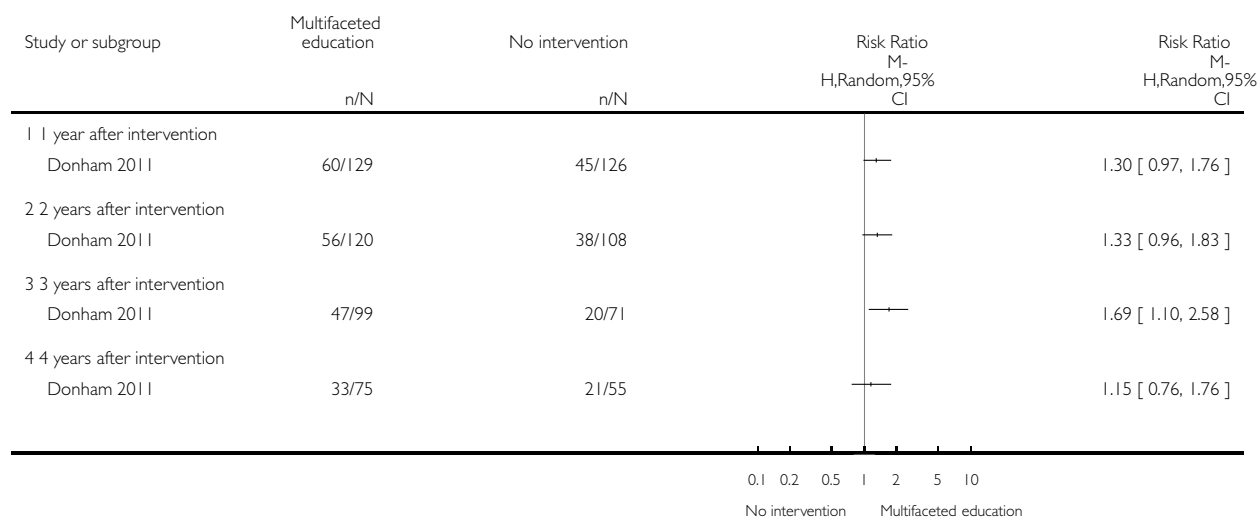


Analysis 3.1. Comparison 3 Education versus no intervention, Outcome 1 Use of RPE most of the time.

Review: Behavioural interventions to promote workers' use of respiratory protective equipment

Comparison: 3 Education versus no intervention

Outcome: 1 Use of RPE most of the time

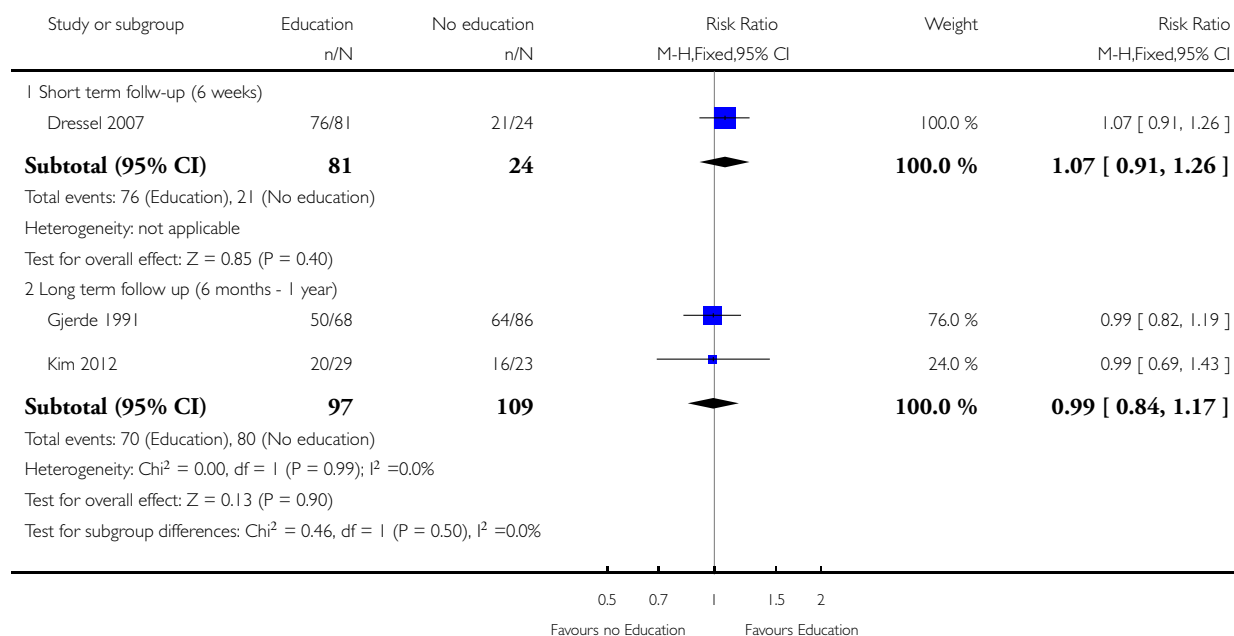


Analysis 3.2. Comparison 3 Education versus no intervention, Outcome 2 Reported RPE use among farmers.

Review: Behavioural interventions to promote workers' use of respiratory protective equipment

Comparison: 3 Education versus no intervention

Outcome: 2 Reported RPE use among farmers

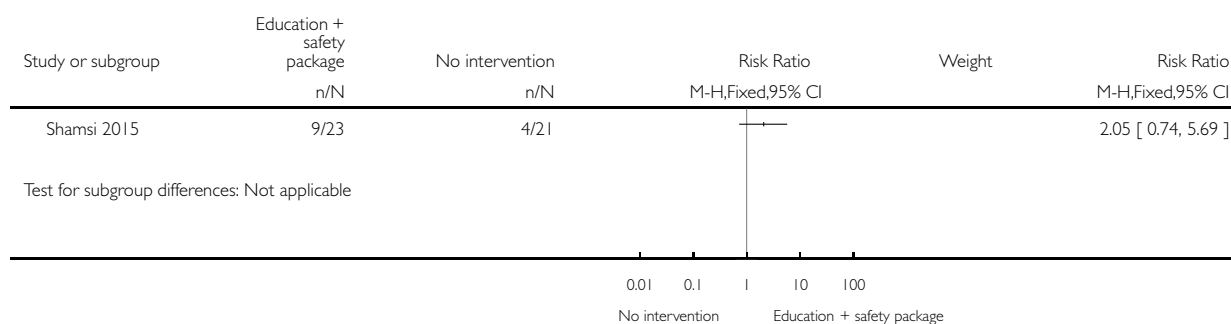


Analysis 3.3. Comparison 3 Education versus no intervention, Outcome 3 Using safety mask while working.

Review: Behavioural interventions to promote workers' use of respiratory protective equipment

Comparison: 3 Education versus no intervention

Outcome: 3 Using safety mask while working

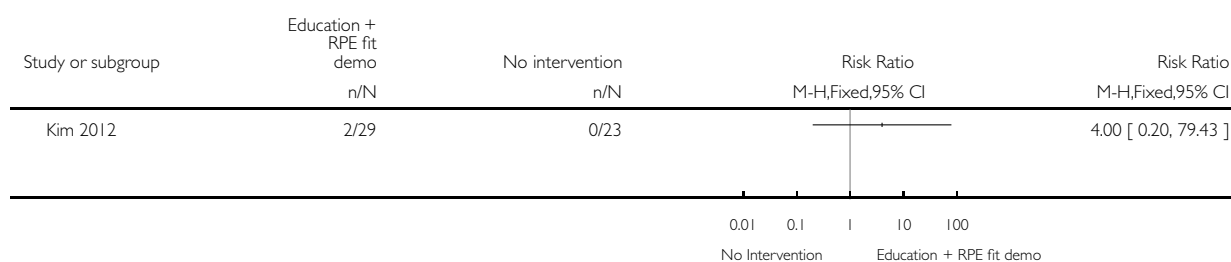


Analysis 3.4. Comparison 3 Education versus no intervention, Outcome 4 Use of RPE (PAPR).

Review: Behavioural interventions to promote workers' use of respiratory protective equipment

Comparison: 3 Education versus no intervention

Outcome: 4 Use of RPE (PAPR)

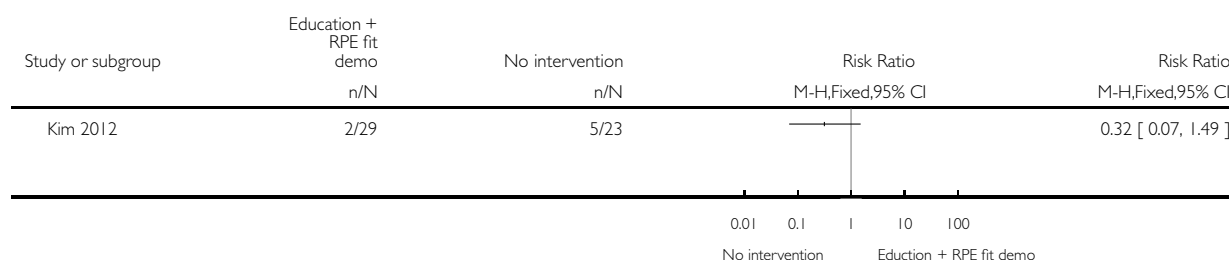


Analysis 3.5. Comparison 3 Education versus no intervention, Outcome 5 Fit tested for N95.

Review: Behavioural interventions to promote workers' use of respiratory protective equipment

Comparison: 3 Education versus no intervention

Outcome: 5 Fit tested for N95

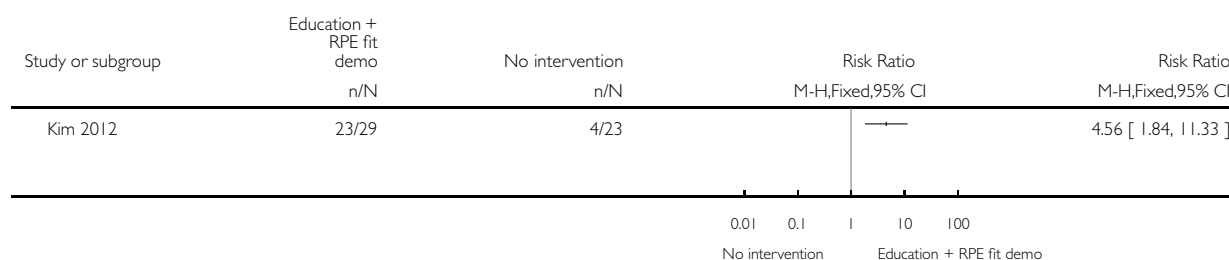


Analysis 3.6. Comparison 3 Education versus no intervention, Outcome 6 Use of N95 mask.

Review: Behavioural interventions to promote workers' use of respiratory protective equipment

Comparison: 3 Education versus no intervention

Outcome: 6 Use of N95 mask

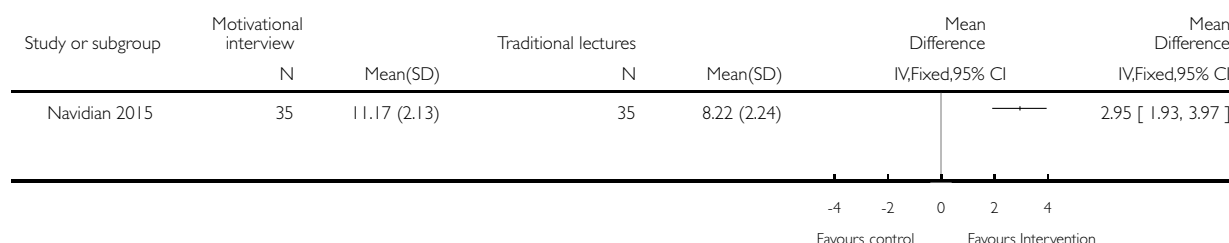


Analysis 4.1. Comparison 4 Motivational interview-based education versus traditional lectures, Outcome 1 Use of RPE as part of full-body PPE.

Review: Behavioural interventions to promote workers' use of respiratory protective equipment

Comparison: 4 Motivational interview-based education versus traditional lectures

Outcome: 1 Use of RPE as part of full-body PPE



ADDITIONAL TABLES

Table 1. Details of interventions in included studies

Studies	Intervention details						Controls
	Education and training	Demonstration of respirator	Fit test	Audit	Session duration	Follow-up time	
Carrico 2007	Supplemental training in addition to classroom training, using a visual demonstration of respiration particle dispersion involving the use of a patient bio-simulator	Yes	No	Yes, observations in practice	No details	3 months	Standard classroom teaching
Donham 2011	Education: newsletter, website, yearly group educational session	Yes	Yes	Yes, annual on-farm safety audit with set standards; financial incentives	No details	4 years	No intervention

Table 1. Details of interventions in included studies (Continued)

Dressel 2007	2 educational sessions	Yes	No	No	2 to 2.5 hours	4 to 6 weeks	No intervention
Eckerman 2002	Interactive training intervention, provided basic respiratory protection information	No	No	No	No details	2 weeks	Reading training
Hung 2015	Conventional PPE training plus computer-simulated training using the proposed simulation program	Yes	No	No	Not mentioned	1 week for the control group and 2 weeks for the intervention group	Conventional PPE training
Gjerde 1991	6 educational home study modules and 1 evening session in which respirator use and gas measurement were demonstrated	Yes	No	No	No details	1 year	No intervention without any detail
Hannum 1996	One-on-one training by the hospital hygienist, plus fit test Classroom instruction and demonstration by infection control nurses	Yes	Yes	No	No details	3 months	No formal training
Kim 2012	Education on work-related asthma and agricultural causes; spirometry testing; respi-	Yes	Yes	No	1 evening	6 months	No intervention

Table 1. Details of interventions in included studies (Continued)

	rator demonstrations and fit testing; exposure reduction strategies; barriers to PPE use						
Myers 1995	Training on donning the RPE using the +/- fit check	No	Yes	No	2 days	3 days	Training on donning the RPE without using the +/- fit check
Navidian 2015	4 educational sessions based on motivational group interviewing	No	No	No	Twice a week	12 weeks	1-hour safety education sessions that were conducted as traditional lectures
Or 2012	Conventional quantitative PortaCount fit test training	No	Intervention Group A and B: yes Intervention Group C: no	No	No details	No details	No training
Parkinson 1989	4 educational sessions	Unclear	Unclear	No	No details	6 months	No intervention
Perry 2003	Educational sessions targeting 4 educational messages in groups of 100 people	No	No	No	3 hours	6 months	Standard re-certification meeting
Shamsi 2015	Received a free package containing a safety helmet with a tailored message affixed to it, a dust mask and safety gloves, and an educational pam-	No	No	No	Not mentioned	4 weeks	No training

Table 1. Details of interventions in included studies (Continued)

	phlet						

PPE: personal protective equipment

APPENDICES

Appendix I. MEDLINE (PubMed) search strategy

#1	“respiratory protection” OR “respiratory protective” OR respirator OR respirators OR “personal protective equipment” OR “personal protective equipments” OR “Respiratory Protective Devices”[Mesh] OR ((personal protect*[tw] OR worker protect*[tw] OR workers protect*[tw] OR protective measure*[tw]) AND (dust[tw] OR dusts[tw] OR mist[tw] OR mists[tw] OR vapor*[tw] OR vapour*[tw] OR fog[tw] OR fogs[tw] OR fume[tw] OR fumes[tw] OR smoke[tw] OR smokes*[tw] OR solvents[tw] OR volatile[tw] OR chemical*[tw] OR biological*[tw] OR SARS[tw] OR hazardous substance*[tw] OR hazardous material*[tw] OR dangerous substance*[tw] OR asbestos*[tw] OR particle*[tw] OR nanoparticle*[tw]))
#2	work[tw] OR works*[tw] OR work*[tw] OR worka*[tw] OR worke*[tw] OR workg*[tw] OR worki*[tw] OR workl*[tw] OR workp*[tw] OR occupation*[tw] OR job[tw] OR jobs [tw] OR employee*[tw] OR organisation*[tw] OR organization*[tw] OR laborer*[tw] OR labourer*[tw] OR construction industry[tw] OR firefight*[tw] OR miners[tw] OR fishing[tw] OR mining[tw] OR constructors[tw] OR “Agriculture”[Mesh] OR “Industry”[Mesh] OR “Occupational Groups”[Mesh] OR “Health Occupations”[Mesh]
#3	training[tw] OR program[tw] OR programs[tw] OR strategy[tw] OR strategies[tw] OR advise*[tw] OR adviso*[tw] OR guidelines[tw] OR behav*[tw] OR intervention*[tw] OR attitude*[tw] OR promot*[tw] OR safety culture[tw] OR safety awareness[tw] OR safety climate[tw] OR cognitive model*[tw] OR maintenance[tw] OR fit testing[tw] OR fit test*[tw] OR incentive*[tw] OR supervis*[tw] OR positive reinforcement[tw] OR social cognitive[tw] OR social model* [tw] OR health belief model*[tw] OR reasoned action[tw] OR frequent feedback[tw] OR organizational polic*[tw] OR organisational polic*[tw]
#4	penalty[tw] OR penalties[tw] OR enforcement[tw] OR sanction[tw] OR sanctions[tw] OR fines[tw] OR warning[tw] OR warnings[tw] OR feedback[tw] OR “legislation and jurisprudence” [sh] OR legislation[tw] OR legislative[tw] OR regulations[tw] OR regulative[tw]
#5	#1 AND #2 AND (#3 OR #4)

Appendix 2. Embase search strategy

#1	(respiratory NEXT/1 protect* OR respirator OR respirators OR 'gas mask'):de,ab,ti
#2	(personal NEXT/2 protect* OR worker* NEAR/2 protect* OR protective NEXT/1 measure*):de,ab,ti
#3	'solvent'/exp OR 'dust'/exp OR 'severe acute respiratory syndrome':de OR 'dangerous goods':de OR 'volatile organic compound':de OR asbestos:de
#4	(sars OR dust* OR mist OR mists OR vapor* OR vapour* OR fog OR fogs OR fume OR fumes OR smoke OR smokes OR solvents OR volatile OR chemical* OR biological* OR 'hazardous substances' OR 'hazardous material' OR 'dangerous substances' OR asbestos* OR particle* OR nanoparticle* OR gas):de,ab,ti
#5	#3 OR #4
#6	#1 OR (#2 AND #5)
#7	'construction work'/exp OR 'mining'/exp OR 'fishing'/exp OR 'agriculture'/exp OR 'nonmedical occupations'/exp OR 'health care personnel'/exp OR 'worker'/de OR 'industry'/exp OR 'work'/exp
#8	(work* OR occupation* OR job OR jobs OR employee* OR organisation* OR organization* OR laborer* OR labourer* OR 'construction industry' OR firefight* OR miners OR fishing OR mining OR constructors OR agriculture OR industry OR 'occupational groups' OR 'health occupations'):de,ab,ti
#9	#7 OR #8
#10	'feedback system'/exp OR 'practice guideline'/exp OR 'behavior change'/exp OR 'policy'/de OR 'punishment'/de OR 'law enforcement'/exp
#11	(training OR program OR programs OR strategy OR strategies OR advise* OR adviso* OR guidelines OR guidance OR behav* OR intervention* OR attitude* OR promot* OR 'safety culture' OR 'safety awareness' OR 'safety climate' OR cognitive NEXT/1 model* OR maintenance OR fit NEXT/1 test* OR incentive* OR supervis* OR 'positive reinforcement' OR 'social cognitive' OR social NEXT/1 model* OR 'health belief' NEXT/1 model* OR 'reasoned action' OR 'frequent feedback' OR organizational NEXT/1 polic* OR organisational NEXT/1 polic*):de,ab,ti
#12	(penalty OR penalties OR enforcement OR sanction OR sanctions OR fines OR warning OR warnings OR feedback OR legislation OR legislative OR regulations OR regulative OR 'labour inspection'):de,ab,ti
#13	#10 OR #11 OR #12
#14	#6 AND #9 AND #13
#15	#14 AND [embase]/lim NOT [medline]/lim

Appendix 3. CENTRAL search strategy

#1	MeSH descriptor: [Respiratory Protective Devices] explode all trees
#2	MeSH descriptor: [Masks] this term only
#3	“respiratory protection” or “respiratory protective” or respirator or respirators or “personal protective equipment” or “personal protective equipments”:ti,ab,kw (Word variations have been searched)
#4	#1 OR #2 OR #3
#5	personal next protect* or worker next protect* or workers next protect* or protective next measure*:ti,ab,kw (Word variations have been searched)
#6	MeSH descriptor: [Air Pollutants, Occupational] explode all trees
#7	MeSH descriptor: [Particulate Matter] explode all trees
#8	dust* or mist or mists or vapor* or vapour* or fog or fogs or fume or fumes or smoke or smokes or solvents or volatile or chemical* or biological* or SARS or hazardous next substance* or hazardous next material* or dangerous next substance* or asbestos* or particle* or nanoparticle*:ti,ab,kw (Word variations have been searched)
#9	#6OR #7 OR #8
#10	#5 AND #9
#11	work* or occupation* or job or jobs or employee* or organisation* or organization* or laborer* or labourer* or construction next industry or firefight* or miners or fishing or mining or constructors:ti,ab,kw (Word variations have been searched)
#12	MeSH descriptor: [Agriculture] explode all trees
#13	MeSH descriptor: [Industry] explode all trees
#14	MeSH descriptor: [Occupational Groups] explode all trees
#15	MeSH descriptor: [Health Occupations] explode all trees
#16	#12 OR #13 OR #14 OR #15
#17	#4 AND #16
#18	#10 OR #17
#19	training or program or programs or strategy or strategies or advise* or adviso* or guidelines or behav* or intervention* or attitude* or promot* or safety next culture or safety next awareness or safety next climate or cognitive next model* or maintenance or fit next test* or incentive* or supervis* or positive next reinforcement or social next cognitive or social next model* or health next belief next model* or reasoned next action or frequent next feedback or organizational next polic*:ti,ab,kw (Word variations have been searched)

(Continued)

#20	penalty or penalties or enforcement or sanction or sanctions or fines or warning or warnings or feedback or legislation or legislative or regulation* or regulative:ti,ab,kw (Word variations have been searched)
#21	#19 OR #20
#22	#18 AND #21 (24) > 22 Central Trials references

Cochrane Central Register of Controlled Trials: Issue 10 of 12, October 2013; 2013-11-20/L

#1	MeSH descriptor: [Respiratory Protective Devices] explode all trees
#2	MeSH descriptor: [Masks] this term only
#3	"respiratory protection" or "respiratory protective" or respirator or respirators or "personal protective equipment" or "personal protective equipments":ti,ab,kw
#4	#1 OR #2 OR #3
#5	personal next protect* or worker next protect* or workers next protect* or protective next measure*:ti,ab,kw
#6	MeSH descriptor: [Air Pollutants, Occupational] explode all trees
#7	MeSH descriptor: [Particulate Matter] explode all trees
#8	dust* or mist or mists or vapor* or vapour* or fog or fogs or fume or fumes or smoke or smokes or solvents or volatile or chemical* or biological* or SARS or hazardous next substance* or hazardous next material* or dangerous next substance* or asbestos* or particle* or nanoparticle*:ti,ab,kw
#9	#6 OR #7 OR #8
#10	#5 AND #9
#11	work* or occupation* or job or jobs or employee* or organisation* or organization* or laborer* or labourer* or construction next industry or firefight* or miners or fishing or mining or constructors:ti,ab,kw
#12	MeSH descriptor: [Agriculture] explode all trees
#13	MeSH descriptor: [Industry] explode all trees
#14	MeSH descriptor: [Occupational Groups] explode all trees
#15	MeSH descriptor: [Health Occupations] explode all trees
#16	#11 OR #12 OR #13 OR #14 OR #15
#17	#4 AND #16

(Continued)

#18	#10 OR #17
#19	training or program or programs or strategy or strategies or advise* or adviso* or guidelines or behav* or intervention* or attitude* or promot* or safety next culture or safety next awareness or safety next climate or cognitive next model* or maintenance or fit next test* or incentive* or supervis* or positive next reinforcement or social next cognitive or social next model* or health next belief next model* or reasoned next action or frequent next feedback or organizational next polic*:ti,ab,kw
#20	penalty or penalties or enforcement or sanction or sanctions or fines or warning or warnings or feedback or legislation or legislative or regulation* or regulative:ti,ab,kw
#21	#19 OR #20
#22	#18 AND #21 (134) > 60 Central Trials references

Appendix 4. CINAHL search strategy

#	Query	Limiters/Expanders	Last Run Via
S28	S24 AND [embase]/lim NOT [med-line]/lim	Search modes - SmartText Searching	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text
S27	S24 AND [embase]/lim NOT [med-line]/lim	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text
S26	S24 AND [embase]/lim	Search modes - SmartText Searching	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text
S25	S24 AND [embase]/lim	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text
S24	S10 AND S15 AND S22	Search modes - SmartText Searching	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text

(Continued)

S23	S10 AND S15 AND S22	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text
S22	S17 OR S19 OR S21	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text
S21	(penalty OR penalties OR enforcement OR sanction OR sanctions OR fines OR warning OR warnings OR feedback OR legislation OR legislative OR regulations OR regulative OR 'labour inspection'): MW,AB,TI	Search modes - SmartText Searching	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text
S20	(penalty OR penalties OR enforcement OR sanction OR sanctions OR fines OR warning OR warnings OR feedback OR legislation OR legislative OR regulations OR regulative OR 'labour inspection'): MW,AB,TI	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text
S19	(training OR program OR programs OR strategy OR strategies OR advise* OR adviso* OR guidelines OR guidance OR behav* OR intervention* OR attitude* OR promot* OR 'safety culture' OR 'safety awareness' OR 'safety climate' OR cognitive NEXT/1 model* OR maintenance OR fit NEXT/1 test* OR incentive* OR supervis* OR 'positive reinforcement' OR 'social cognitive' OR social NEXT/1 model* OR 'health belief' NEXT/1 model* OR 'reasoned action' OR 'frequent feedback' OR organizational NEXT/1 polic* OR organisational NEXT/1 polic*):MW,AB,TI	Search modes - SmartText Searching	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text
S18	(training OR program OR programs OR strategy OR strategies OR advise* OR adviso* OR guidelines OR guidance OR behav* OR intervention* OR attitude* OR promot* OR 'safety culture' OR 'safety awareness' OR 'safety climate' OR cognitive NEXT/1 model* OR maintenance OR fit NEXT/1 test* OR incentive* OR supervis* OR 'positive re-	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text

(Continued)

	inforcement' OR 'social cognitive' OR social NEXT/1 model* OR 'health belief' NEXT/1 model* OR 'reasoned action' OR 'frequent feedback' OR organizational NEXT/1 polic* OR organisational NEXT/1 polic*):MW,AB,TI		
S17	'feedback system'/exp OR 'practice guideline'/exp OR 'behavior change'/exp OR 'policy'/de OR 'punishment'/de OR 'law enforcement'/exp	Search modes - SmartText Searching	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text
S16	'feedback system'/exp OR 'practice guideline'/exp OR 'behavior change'/exp OR 'policy'/de OR 'punishment'/de OR 'law enforcement'/exp	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text
S15	S12 OR S14	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text
S14	(work* OR occupation* OR job OR jobs OR employee* OR organisation* OR organization* OR laborer* OR labourer* OR 'construction Industry' OR firefight* OR miners OR fishing OR mining OR constructors OR agriculture OR industry OR 'occupational groups' OR 'health occupations'):MW,AB,TI	Search modes - SmartText Searching	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text
S13	(work* OR occupation* OR job OR jobs OR employee* OR organisation* OR organization* OR laborer* OR labourer* OR 'construction Industry' OR firefight* OR miners OR fishing OR mining OR constructors OR agriculture OR industry OR 'occupational groups' OR 'health occupations'):MW,AB,TI	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text
S12	'construction work'/exp OR 'mining'/exp OR 'fishing'/exp OR 'agriculture'/exp OR 'nonmedical occupations'/exp OR 'health care personnel'/exp OR 'worker'/de OR 'industry'/exp OR 'work'/exp	Search modes - SmartText Searching	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text

(Continued)

S11	'construction work'/exp OR 'mining'/exp OR 'fishing'/exp OR 'agriculture'/exp OR 'nonmedical occupations'/exp OR 'health care personnel'/exp OR 'worker'/de OR 'industry'/exp OR 'work'/exp	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text
S10	S2 OR (S4 AND S9)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text
S9	S6 OR S8	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text
S8	(sars OR dust* OR mist OR mists OR vapor* OR vapour* OR fog OR fogs OR fume OR fumes OR smoke OR smokes OR solvents OR volatile OR chemical* OR biological* OR 'hazardous substances' OR 'hazardous material' OR 'dangerous substances' OR asbestos* OR particle* OR nanoparticle* OR gas):MW,AB,TI	Search modes - SmartText Searching	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text
S7	(sars OR dust* OR mist OR mists OR vapor* OR vapour* OR fog OR fogs OR fume OR fumes OR smoke OR smokes OR solvents OR volatile OR chemical* OR biological* OR 'hazardous substances' OR 'hazardous material' OR 'dangerous substances' OR asbestos* OR particle* OR nanoparticle* OR gas):MW,AB,TI	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text
S6	'solvent'/exp OR 'dust'/exp OR 'severe acute respiratory syndrome':MW OR 'dangerous goods':SU OR 'volatile organic compound':MW OR asbestos:MW	Search modes - SmartText Searching	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text
S5	'solvent'/exp OR 'dust'/exp OR 'severe acute respiratory syndrome':MW OR 'dangerous goods':SU OR 'volatile organic compound':MW OR asbestos:MW	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text

(Continued)

S4	(personal NEXT/2 protect* OR worker* NEAR/2 protect* OR protective NEXT/1 measure*):MW,AB,TI	Search modes - SmartText Searching	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text
S3	(personal NEXT/2 protect* OR worker* NEAR/2 protect* OR protective NEXT/1 measure*):MW,AB,TI	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text
S2	(respiratory NEXT/1 protect* OR respirator OR respirators OR 'gas mask'):MW,AB,TI	Search modes - SmartText Searching	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text
S1	(respiratory NEXT/1 protect* OR respirator OR respirators OR 'gas mask'):MW,AB,TI	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text

#1 =s2	(respiratory NEXT/1 protect* OR respirator OR respirators OR 'gas mask'): MW,AB,TI
#2 =s4	(personal NEXT/2 protect* OR worker* NEAR/2 protect* OR protective NEXT/1 measure*):MW,AB,TI
#3 =S6	'solvent'/exp OR 'dust'/exp OR 'severe acute respiratory syndrome':MW OR 'dangerous goods':SU OR 'volatile organic compound':MW OR asbestos:MW
#4 =S8	(sars OR dust* OR mist OR mists OR vapor* OR vapour* OR fog OR fogs OR fume OR fumes OR smoke OR smokes OR solvents OR volatile OR chemical* OR biological* OR 'hazardous substances' OR 'hazardous material' OR 'dangerous substances' OR asbestos* OR particle* OR nanoparticle* OR gas):MW,AB,TI
#5 =S9	#3 OR #4
#6 = S10	#1 OR (#2 AND #5) S2 OR (S4 AND S9)
#7 =S12	'construction work'/exp OR 'mining'/exp OR 'fishing'/exp OR 'agriculture'/exp OR 'nonmedical occupations'/exp OR 'health care personnel'/exp OR 'worker'/de OR 'industry'/exp OR 'work'/exp (79)
#8 =S14	(work* OR occupation* OR job OR jobs OR employee* OR organisation* OR organization* OR laborer* OR labourer* OR 'construction Industry' OR firefight* OR miners OR fishing OR mining OR constructors OR agriculture OR industry OR 'occupational groups' OR 'health occupations'):MW,AB,TI (25)
#9 =S15	#7 OR #8 (104) S12 OR S14
#10 =S17	'feedback system'/exp OR 'practice guideline'/exp OR 'behavior change'/exp OR 'policy'/de OR 'punishment'/de OR 'law enforcement'/exp (44)

(Continued)

#11 =S19	(training OR program OR programs OR strategy OR strategies OR advise* OR adviso* OR guidelines OR guidance OR behav* OR intervention* OR attitude* OR promot* OR 'safety culture' OR 'safety awareness' OR 'safety climate' OR cognitive NEXT/1 model* OR maintenance OR fit NEXT/1 test* OR incentive* OR supervis* OR 'positive reinforcement' OR 'social cognitive' OR social NEXT/1 model* OR 'health belief' NEXT/1 model* OR 'reasoned action' OR 'frequent feedback' OR organizational NEXT/1 polic* OR organisational NEXT/1 polic*):MW,AB,TI (0)
#12 =S21	(penalty OR penalties OR enforcement OR sanction OR sanctions OR fines OR warning OR warnings OR feedback OR legislation OR legislative OR regulations OR regulative OR 'labour inspection'):MW,AB,TI (10)
#13 =S22	#10 OR #11 OR #12 (54) S17 OR S19 OR S21
#14 =S24	#6 AND #9 AND #13 S10 AND S15 AND S22
#15 =S26	#14 AND [embase]/lim S24 AND [embase]/lim
#16 =S28	#14 AND [embase]/lim NOT [medline]/lim S24 AND [embase]/lim NOT [medline]/lim

CONTRIBUTIONS OF AUTHORS

Pornpun Sakunkoo (PS), David Koh (DK) and Malinee Laopaiboon (ML) drafted the protocol.

All review authors approved the final version of the protocol.

PS, ML, DK, Yen B Luong Thanh (YLT) and Hla Moe (HM) carried out study selection.

PS, YLT, HM, DK and ML carried out data extraction.

ML, YLT carried out data analysis.

YLT, ML and DK wrote the first draft of the review.

YLT, ML and DK revised the draft of the review.

All review authors approved the final version.

DECLARATIONS OF INTEREST

Malinee Laopaiboon: I have received an honorarium from Thailand Research Fund, a non-profit organization, to conduct this Cochrane review.

Bao Yen Luong Thanh: None known.

Pornpun Sakunkoo: None known.

David Koh: None known.

Hla Moe: None known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have modified the criteria for the assessment of risk of bias for RCTs and CBA studies. We planned to use the standard Cochrane risk of bias tool for RCTs and the [Downs 1998](#) tool for CBA studies. Instead we used the Cochrane risk of bias tool for all studies because the Cochrane risk of bias tool could be adapted to the CBA studies. We did not specify in our protocol when we would consider a study have a high, low or unclear risk of bias overall. We think the distinction makes our GRADE assessment more transparent.

INDEX TERMS

Medical Subject Headings (MeSH)

*Workplace; Controlled Before-After Studies; Farmers; Health Personnel; Health Promotion [*methods]; Interrupted Time Series Analysis; Motivational Interviewing; Occupations; Randomized Controlled Trials as Topic; Respiratory Protective Devices [*utilization]

MeSH check words

Humans



Cochrane
Library

Cochrane Database of Systematic Reviews

Antibiotics for infection prevention after excision of the cervical transformation zone (Review)

Kietpeerakool C, Chumworathayi B, Thinkhamrop J, Ussahgij B, Lumbiganon P

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	4
BACKGROUND	7
OBJECTIVES	7
METHODS	7
RESULTS	10
Figure 1.	12
Figure 2.	14
DISCUSSION	16
AUTHORS' CONCLUSIONS	17
ACKNOWLEDGEMENTS	18
REFERENCES	18
CHARACTERISTICS OF STUDIES	20
DATA AND ANALYSES	27
Analysis 1.1. Comparison 1 Prolonged vaginal discharge, Outcome 1 Number of participants who experienced prolonged vaginal discharge.	28
Analysis 2.1. Comparison 2 Excessive vaginal bleeding, Outcome 1 Number of participants who had to be admitted for postoperative bleeding.	29
Analysis 3.1. Comparison 3 Fever, Outcome 1 Number of participants who developed fever.	30
Analysis 4.1. Comparison 4 Lower abdominal pain, Outcome 1 Number of participants who experienced lower abdominal pain.	30
Analysis 5.1. Comparison 5 Adverse effects, Outcome 1 Number of participants who experienced any adverse effects related to antibiotics.	31
Analysis 6.1. Comparison 6 Unscheduled medical consultant, Outcome 1 Number of participants who received additional medical consultant (for any reasons).	31
Analysis 7.1. Comparison 7 Additional self-medication, Outcome 1 Number of participants who had additional self-medication.	32
ADDITIONAL TABLES	32
APPENDICES	33
CONTRIBUTIONS OF AUTHORS	37
DECLARATIONS OF INTEREST	38
SOURCES OF SUPPORT	38
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	38

Antibiotics for infection prevention after excision of the cervical transformation zone

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ABSTRACT

Background

Excision of the transformation zone of the cervix is the most commonly used approach to treat cervical precancerous lesions (cervical intraepithelial neoplasia (CIN)) to reduce the risk of developing cervical cancer. As the excision of the transformation zone leaves a raw area on the cervix, there is a risk of infection following the procedure. The incidence of infection after cold knife conization (CKC) is 36%, whereas the incidence for large loop excision of the transformation zone (LLETZ, also known as loop electrical excision procedure (LEEP)) is much lower (0.8% to 14.4%). Prophylactic antibiotics may prevent an infection developing and are often prescribed for CKC. However, there are no formal recommendations regarding the use of prophylactic antibiotics for infection prevention in women undergoing surgical excisional treatment for cervical precancerous lesions.

Objectives

To evaluate the effectiveness and safety of antibiotics for infection prevention following excision of the cervical transformation zone.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2016, Issue 4), MEDLINE, Embase, LILACS to May 2016. We also checked registers of clinical trials, citation lists of included studies, key textbooks and previous systematic reviews for potentially relevant studies

Selection criteria

We included randomised controlled trials (RCTs) evaluating the effectiveness and safety of prophylactic antibiotics versus a placebo or no treatment in women having excision of the cervical transformation zone, regardless of the type of surgical excisional method used.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. Two review authors independently selected potentially relevant trials, extracted data, and assessed risk of bias, compared results and resolved disagreements by discussion. We contacted investigators for additional data, where possible.

Main results

Of the 370 records that we identified as a result of the search (excluding duplicates), we regarded six abstracts and titles as potentially relevant studies. Of these six studies, three met the inclusion criteria involving 708 participants; most trials were at moderate or high risk of bias (risk mainly due to lack of blinding and high rate of incomplete data). We did not identify any ongoing trials. Although all included studies had been published in peer-reviewed journals at the time of the search and data extraction, numerical data regarding the outcome measured in one trial involving 77 participants were insufficient for inclusion in a meta-analysis.

The difference in the rates of prolonged vaginal discharge or presumed cervicitis (one study; 348 participants; risk ratio (RR), 1.29; 95% confidence interval (CI) 0.72 to 2.31; low-quality evidence) and severe vaginal bleeding (two studies; 638 participants; RR 1.21; 95% CI 0.52 to 2.82; very low-quality evidence) among the two comparison groups did not reach the level for clinically important effect. In addition, there was no difference in adverse events related to antibiotics i.e. nausea/vomiting, diarrhoea, and headache among the two comparison groups (two studies; 638 participants; RR 1.69; 95% CI 0.85 to 3.34; very low-quality evidence). There were no differences in the incidence of fever (RR, 2.23; 95% CI 0.20 to 24.36), lower abdominal pain (RR, 1.03; 95% CI 0.61 to 1.72), unscheduled medical consultation (RR 2.68, 95% CI 0.97 to 7.41), and additional self-medication (RR 1.22; 95% CI 0.56 to 2.67) between the two comparison groups (one study; 290 participants; low to very low-quality evidence).

Authors' conclusions

As only limited data are available from three trials with overall moderate to high risk of bias, there is insufficient evidence to support use of antibiotics to reduce infectious complications following excision of the cervical transformation zone. In addition, there were minimal data about antibiotic-related adverse events and no information on the risk of developing antibiotic resistance. Antibiotics given for infection prevention after excision of the cervical transformation zone should only be used in the context of clinical research, to avoid unnecessary prescription of antibiotics and to prevent further increases in antibiotic resistance.

PLAIN LANGUAGE SUMMARY

Prophylactic antibiotics to prevent infection after cervical excision

Background

Pre-cancerous cervical lesions can be treated by either excision or destruction of the abnormal cells from the cervix, to reduce the risk of developing cervical cancer in the future. The advantage of excisional treatment is that the abnormal cells are removed, rather than destroyed, so tissue can be sent for detailed examination to confirm the diagnosis histologically and make sure the affected area has been completely removed. As the excision of the transformation zone leaves a raw area on the cervix, there is a risk of getting an infection following the procedure. Antibiotics are sometimes given before surgical procedures to prevent infection developing (prophylactic), rather than to treat an existing infection. However, prophylactic antibiotics may not be necessary or effective. In addition, antibiotics can cause side effects (adverse events). Importantly, there are increasing concerns about antibiotic over-use promoting antibiotic resistance in bacteria.

Review question

Do prophylactic antibiotics prevent infection in women undergoing excision of the cervical transformation zone and what are the side effects?

Main findings

We searched the literature to May 2016 and found three published randomised trials that met the review inclusion criteria. We did not identify any ongoing trials. The three included studies involved 708 participants who had undergone excisional treatment to the cervix (known as laser or large loop excision of transformation zone (LLETZ) or loop electrosurgical excision procedure (LEEP)). Two studies tested an antimicrobial vaginal pessary versus no treatment; the other tested oral antibiotics compared with placebo. We found that there was no benefit to prophylactic antibiotics after LLETZ to reduce or prevent prolonged vaginal discharge, severe vaginal bleeding, fever, lower abdominal pain, unscheduled medical consultation, and additional self-medication. There was little information on antibiotic-related adverse effects. The limited evidence available does not support routinely giving antibiotics for infection prevention after LLETZ. As there are growing concerns with antibiotic resistance, antibiotics for infection prevention after excision of the cervical transformation zones should only be used in the context of clinical trials.

Quality of the evidence

The quality of the evidence regarding prophylactic antibiotics for preventing severe vaginal bleeding, fever, and adverse events was very low, with evidence from other comparisons being of low quality.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Antibiotics compared with placebo or no treatment for infection prevention after excision of the cervical transformation zone						
Patient or population: Women undergoing excision of the cervical transformation zone for cervical neoplasia						
Settings: Outpatients setting, the colposcopy clinic						
Intervention: Prophylactic antibiotics						
Comparison: Placebo or no treatment						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	[Placebo or no treatment]	[Antibiotics]				
Number of participants who experienced prolonged vaginal discharge Follow-up period: 2 weeks after the procedure	103 per 1000	133 per 1000 (74 to 238)	RR 1.29 (0.72 to 2.31)	348 (1 study)	⊕⊕○○ low ^{1,3}	
Number of participants who had to be admitted for post-procedure bleeding Follow-up period: 2-3 weeks after the procedure	31 per 1000	38 per 1000 (16 to 87)	RR 1.21 (0.52 to 2.82)	638 (2 studies)	⊕○○○ very low ^{1,2,3,4}	
Number of participants who developed fever Follow-up period: 3 weeks after the procedure	7 per 1000	16 per 1000 (1 to 171)	RR 2.23 (0.20 to 24.36)	290 (1 study)	⊕○○○ very low ^{2,3,4,5}	

Number of participants who experienced lower abdominal pain Follow-up period: 3 weeks after the procedure	163 per 1000	168 per 1000 (99 to 289)	RR 1.03 (0.61 to 1.72)	290 (1 study)	⊕⊕○○ low ^{2,3}
Number of participants who experienced any adverse effects related to antibiotics Follow-up period: 2-3 weeks after the procedure	37 per 1000	63 per 1000 (31 to 124)	RR 1.69 (0.85 to 3.34)	638 (2 studies)	⊕○○○ very low ^{1,2,3,4}
Number of participants who received additional medical consultant (for any reasons) Follow-up period: 3 weeks after the procedure	33 per 1000	88 per 1000 (32 to 255)	RR 2.68 (0.97 to 7.41)	290 (1 study)	⊕⊕○○ low ^{2,3}
Number of participants who had additional self-medication Follow-up period: 3 weeks after the procedure	72 per 1000	88 per 1000 (40 to 192)	RR 1.22 (0.56 to 2.67)	290 (1 study)	⊕⊕○○ very low ^{1,2,3}

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk Ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹Based on the high risk of attrition bias (high rate of incomplete participants' record charts)

²Based on high risk of detection bias (mainly due to lack of blinding of participants)

³The analyses were not performed on an intention-to-treat basis

⁴Small number of events in the analyses

⁵Sparseness of data

BACKGROUND

Description of the condition

Cervical cancer remains a major world public health problem, as there are 500,000 new cases diagnosed and 275,000 deaths from cervical cancer occurring among women worldwide each year (Wiebe 2012). Many cervical cancers can be prevented through screening programs designed to detect and treat cervical cancer precursors. At the present, cervical intraepithelial neoplasia (CIN) grade 2 to 3, or the so-called 'high-grade squamous intraepithelial lesions (HSILs)' and adenocarcinoma in situ (AIS) are acknowledged as precancerous lesions of squamous cell carcinoma and adenocarcinoma of the uterine cervix, respectively (Massad 2013).

Excision of the cervical transformation zone, an area where the majority of abnormalities occur, is the most commonly used approach to treat cervical precancerous lesions. The major advantage of excisional treatment is that the affected area is removed, so the excised specimen can be sent for detailed pathological examination to determine the severity of the lesion and ensure that abnormal lesion has been completely removed. The common surgical techniques for excision of the cervical transformation zone include large loop excision of the transformation zone (LLETZ), cold-knife conization (CKC), and laser conization (LC). The terms LLETZ and loop electrosurgical excision procedure (LEEP) both have been used to describe a technique to excise the transformation zone using a fine wire loop with an electrical current (diathermy). This technique is also referred to as loop diathermy excision, loop biopsy, and loop cone. Current evidence obtained from a Cochrane review conducted to evaluate the effectiveness of various surgical techniques for treating cervical intraepithelial neoplasia concludes that there is no single method that is a superior surgical technique for treating cervical intraepithelial neoplasia (Martin-Hirsch 2013).

Genital infections, as defined by cervical tenderness, fever, or wound infection requiring antibiotic therapy, have been reported to be as high as 36% after CKC (Janthanaphan 2009) and may have serious complications such as sepsis from lung and liver abscesses (Treszezamsky 2010). LLETZ has a lower incidence of infectious complications ranging from 0.8% to 14.4% (Kietpeerakool 2007; Lopez 1994; Mints 2006; Mitchell 1998; Prendiville 1989; Takac 1999). The incidence of infectious complications after excision of the cervical transformation zone would be much higher, if delayed vaginal bleeding (occurring after 24 hours of the procedure) and offensive discharge are also included (Chamot 2010). However, excisional procedures are often associated with prolonged vaginal discharge, which is not necessarily infective, but may be due to the healing processes and oedema secondary to the procedure.

The American College of Obstetricians and Gynecologists (ACOG) recommends single-dose antibiotic prophylactic protocols using cephalosporin, ampicillin, gentamicin, metronidazole or antibiotics in the quinolone group prior to some major surgical procedures (ACOG 2009). However, there are no formal recommendations regarding the use of prophylactic antibiotics for LC, CKC or LLETZ, which are outpatient treatments that could be considered as contaminated procedures, since the vagina is not sterile. Therefore, the use of prophylactic antibiotics may be considered (Chamot 2010).

How the intervention might work

The excision of the transformation zone leaves a raw surface on the cervix, where vaginal flora or introduced bacteria may initiate infections. Theoretically, prophylactic antibiotics would prevent these infections by eliminating these bacteria at an early stage. Several studies have shown that prophylactic antibiotics can reduce the risk of infections among women undergoing intrauterine device insertion, surgical abortion, and repair of severe perineal tear (Buppasiri 2014; Grimes 1999; Sawaya 1996).

Why it is important to do this review

Standard clinical practice guidelines regarding the effectiveness and safety of prophylactic antibiotics for infection prevention after excision of the cervical transformation zone are lacking. A previous systematic review conducted to determine the safety of LLETZ identified that information regarding the use of prophylactic antibiotic therapy for infection prevention was inconsistently reported. Routine antibiotic therapy was described in only three out of 16 included studies (Chamot 2010). This systematic review, looking at the use of prophylactic antibiotics for the prevention of infection following the excision of the cervical transformation zone aims to evaluate the best and current evidence for the use of prophylactic antibiotics in this setting.

OBJECTIVES

To evaluate the effectiveness and safety of antibiotics for infection prevention following excision of the cervical transformation zone.

METHODS

Description of the intervention

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs). We did not include quasi-randomised trials as these may have been subjected to increased bias.

Types of participants

Women of any age undergoing excision of the cervical transformation zone for cervical intraepithelial neoplasia (CIN), irrespective of surgical techniques.

Types of interventions

Prophylactic antibiotics (irrespective of regimens) versus placebo or no treatment.

Classification of antibiotics were as follows (Marjoribanks 2004).

1. Cephalosporins
2. Penicillins
3. Macrolides
4. Fluoroquinolones
5. Sulfonamides
6. Tetracyclines
7. Aminoglycosides
8. Glycopeptides
9. Antiprotozoals
10. Combination drugs

Antibiotic regimen includes the following.

1. Administration route (for example intravenous, intramuscular, oral, vaginal)
2. Number of doses (for example single versus multiple doses)

Types of outcome measures

Primary outcomes

1. Infectious complications (defined as any documented sites of infection identified by cultivation or clinical symptoms and signs, or both), measured as the proportion of participants who developed each of the following within eight weeks of surgery: cervicitis, endometritis, pelvic inflammatory disease, prolonged vaginal discharge, severe vaginal bleeding, lower abdominal pain, fever, and additional antibiotic treatment.

2. Antibiotic resistance

Secondary outcomes

1. Adverse effects related to antibiotics: classified according to Common Terminology Criteria for Adverse Events (CTCAE 2010) as follows: gastrointestinal disorders (nausea, vomiting, anorexia, diarrhoea); immune system disorders (allergic reaction, anaphylaxis) blood and lymphatic system disorders (leucopenia, anaemia, thrombocytopenia, neutropenia); skin (stomatitis,

mucositis, alopecia, allergy); nervous system disorders; genitourinary; and other side effects not categorised above

2. Unscheduled medical consultant (for any reasons).
3. Additional self-medication.

As the association between vaginal bleeding, offensive vaginal discharge and secondary infection following excision of the cervical transformation zone has been observed in previous reports (Chan 2007; Doyle 1992), we chose severe vaginal bleeding and prolonged vaginal discharge as the surrogates for infectious complication. We did not include urinary tract infections and quality of life (QoL) in this review as these were not directly related to excision of the cervical transformation zone.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 4) in the Cochrane Library, MEDLINE (1946 to May week 1, 2016), Embase (1980 to 2016, week 19), and LILACS (1970 to May, 2016). Appendix 1, Appendix 2, Appendix 3, and Appendix 4 display the search strategies for CENTRAL, MEDLINE, Embase and LILACS, respectively.

Searching other resources

Unpublished and grey literature

We searched the following sources for ongoing trials.

1. ISRCTN registry, metaRegister of Controlled Trials (mRCT <http://www.isrctn.com/page/mrct>).
 2. Physicians Data Query (<https://www.cancer.gov/publications/pdq>).
 3. Clinical trials.gov <http://www.clinicaltrials.gov>.
 4. International Clinical Trials Registry Platform (ICTRP) (<http://www.who.int/ictrp/en/>).
 5. World Health Organization (WHO) International Clinical Trial Registry (<http://apps.who.int/trialsearch/Default.aspx>).
- We searched electronic databases including GreyNet.org (<http://www.greynet.org>), the Ohio College Library Center (OCLC) WorldCat Dissertations and Theses (WorldCat Dissertations; <https://www.oclc.org/support/services/firstsearch/documentation/dbdetails/details/WorldCatDissertations.en.html>) and Index to theses (ProQuest Dissertations & Theses: UK & Ireland) to identify the possible relevant conference abstracts and proceedings.

Handsearching

We handsearched reports of conferences from the following sources.

1. Gynecologic Oncology (Annual Meeting of the Society of Gynecologic Oncology)

2. International Journal of Gynecological Cancer (Annual Meeting of the International Gynecologic Cancer Society)
3. Annual Meeting of the European Society of Medical Oncology (ESMO)
4. Annual Meeting of the British Gynaecological Cancer Society (BGCS)
5. Biennial Meeting of the Asian Society of Gynecologic Oncology (ASGO)
6. Biennial Meeting of Asia and Oceania Federation of Obstetrics and Gynaecology (AOFOG)
7. Biennial Meeting of the European Society of Gynaecologic Oncology (ESGO)

We also checked the citation lists of the included studies and key textbooks for potentially relevant references. We searched for papers in all languages and would have had them translated, if necessary.

Data collection and analysis

Selection of studies

We downloaded all titles and abstracts retrieved by electronic searching to Endnote, and duplicates were removed. Two review authors (CK and BC) independently examined the remaining references. We excluded those studies that did not meet the inclusion criteria and obtained copies of the full text of potentially relevant references. We (CK and BC) independently assessed the eligibility of retrieved papers. We resolved disagreements by discussion and, if there was no consensus, by appeal to a third review author (JT or PL). We documented the reasons for exclusion (see [Excluded studies](#) and [Characteristics of excluded studies](#)).

Data extraction and management

We (CK and BC) abstracted data independently onto a data abstraction form specifically designed for the review. We resolved differences between review authors by discussion or by appeal to a third reviewer (JT or PL), if necessary. The same two review authors independently assessed the quality of the trials and abstracted data using forms specifically designed for the review, according to Cochrane guidelines ([Higgins 2011](#)).

Trial characteristics

1. Method of randomisation
2. Method of allocation concealment
3. Presence or absence of blinding of participants, clinicians and outcome assessors to treatment allocation
4. Number of participants randomised
5. Number of withdrawals (participants excluded from analysis or lost to follow-up) and reasons
6. Whether an intention-to-treat (ITT) analysis was done

7. Duration, timing and location of the study

Characteristics of the study participants

1. Type of an excision of the cervical transformation zone undergone (either by CKC, laser conization, LEEP, LLETZ, or any other excision technique)
2. Inclusion criteria
3. Exclusion criteria
4. Whether the groups of participants were well balanced with regard to prognostic factors

Intervention used

1. Type of antibiotics used
2. Dose
3. Route
4. Single or multiple doses given
5. Duration of course of antibiotics
6. Number and timing of doses

Nature of comparison

1. No treatment, or placebo
2. Route of administration
3. Drug regimen

Outcomes

1. Methods used to measure genital infections
2. Methods used to evaluate adverse effects

Assessment of risk of bias in included studies

We assessed and reported on the methodological risk of bias of the included studies according to Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)), which recommends the explicit reporting of the following individual elements for RCTs.

1. Selection bias: random sequence generation and allocation concealment.
2. Performance bias: blinding of participants and personnel (participants and treatment providers).
3. Detection bias: blinding of outcome assessment.
4. Attrition bias: incomplete outcome data.
5. Reporting bias: selective reporting of outcomes.
6. Other bias

Two review authors (CK, BC) applied the 'Risk of bias' tool independently, and we resolved differences by discussion or by appeal to a third review author (JT or PL). We judged each item as being at high, low or unclear risk of bias as set out in the criteria shown in [Appendix 5](#) ([Higgins 2011](#)). We provided a quote from the study report or a statement as justification for our judgement. We summarised results in a 'Risk of bias' summary figure.

Measures of treatment effect

We used the following measures of the effect of treatment.

1. For dichotomous data (e.g. adverse events or infections), we extracted the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed at endpoint, in order to estimate a risk ratio (RR) with 95% confidence intervals (CIs).

2. For continuous data, we planned to use the mean difference (MD) or standardized mean difference (SMD) with 95% CIs. Where possible RRs of individual studies were combined for meta-analysis using [RevMan 2014](#) software.

Dealing with missing data

We did not impute missing outcome data for the primary outcome and we attempted to contact study authors to obtain missing data. If data were missing to the extent that we could not have included the study in the analysis, we had planned to present the results in a narrative way.

Assessment of heterogeneity

We assessed heterogeneity using visual inspection of the forest plots. We also assessed statistical heterogeneity in each meta-analysis using the I^2 statistic and χ^2 test. We regarded heterogeneity as substantial if the I^2 statistic value was greater than 50%, or there was a low P value (< 0.10) in the χ^2 test for heterogeneity ([Deeks 2001](#); [Higgins 2011](#)). If there was substantial statistical heterogeneity, we planned to carry out subgroup analyses to assess differences between the included studies. However, if there had been clinical, methodological or considerable statistical heterogeneity (I^2 greater than 75%) across included studies, we had planned to use a narrative approach to data synthesis.

Assessment of reporting biases

We had planned to examine funnel plots corresponding to meta-analysis of the primary outcome to assess the potential for small-study effects, such as publication bias, if more than 10 studies were included. If asymmetry had been suggested by a visual assessment, we had planned to perform sensitivity analysis to investigate whether it affected the pooled results. ([Sterne 2011](#)).

Data synthesis

Where feasible, the results were pooled in a meta-analysis. We used the random-effects model with inverse variance weighting for all meta-analyses ([DerSimonian 1986](#)). We performed statistical analysis using [RevMan 2014](#).

1. For dichotomous outcomes, we calculated the RR for each study as well as for the pooled outcome.

2. For continuous outcomes, we calculated and pooled the mean difference between the treatment arms if all trials measured

the outcome on the same scale; otherwise we pooled the standardised mean differences.

We prepared a 'Summary of findings' table to present the results of the meta-analysis, based on the methods described in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Schunemann 2011](#)). For assessments of the overall certainty of evidence for each outcome that includes pooled data from RCTs only, we downgraded the evidence from 'high certainty' by one level for serious (or by two for very serious) study limitations (risk of bias), indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias. The following outcomes were included in the 'Summary of findings' table:

1. prolonged vaginal discharge;
2. postoperative bleeding;
3. fever;
4. abdominal pain;
5. adverse effect related to antibiotic;
6. additional medical support;
7. additional self-medication.

We presented the results of the meta-analysis for the relevant outcomes and adverse events as outlined in the 'Types of outcome measures' section.

Subgroup analysis and investigation of heterogeneity

As we found only a few trials, we did not perform any subgroup analyses. However, we considered factors such as type of excisional techniques (e.g. CKC, LC, or LLETZ/LEEP) and antibiotic regimen prescribed in the interpretation of review findings. In future updates, we will perform subgroup analysis based on these factors, if feasible.

Sensitivity analysis

As we found only three trials, we did not perform any sensitivity analysis. In future updates, if statistical heterogeneity is detected and there are sufficient trials included (greater than 10), we will conduct sensitivity analyses to examine the possible contribution of other clinical or methodological differences between the trials, specifically:

1. trials with adequate methodology versus those with poor methodology;
2. trials which seem to differ from the others in their clinical criteria for defining genital infections.

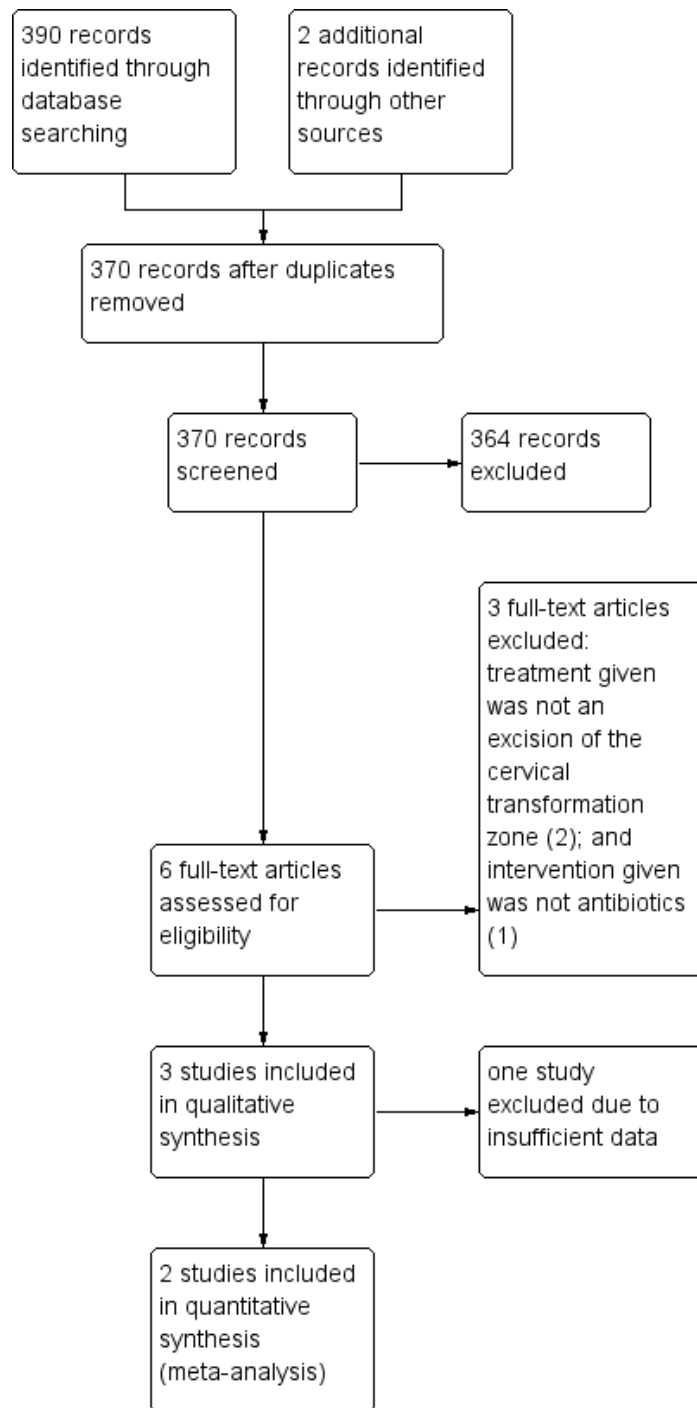
RESULTS

Description of studies

Results of the search

We ran a broad search that yielded 390 references from the combined searches. We checked the reference lists and handsearched journals and congress abstracts, which identified two additional references. We did not identify any ongoing trials. After de-duplication, we screened 370 references and excluded 364 references that obviously did not meet the inclusion criteria. Of the six studies that potentially met the review inclusion, we excluded three studies after reviewing the full texts (Doyle 1992; Gerli 2012; Minorchio 1990) (see [Excluded studies](#) and [Characteristics of excluded studies](#)). [Figure 1](#) displays the PRISMA flowchart for study selection.

Figure 1. Study flow diagram.



Included studies

We found three studies that met the inclusion criteria (Chan 2007; Foden-Shroff 1998; Gornall 1999). See 'Characteristics of included studies' for details of each included study.

Foden-Shroff 1998 was conducted in UK from July 1994 to August 1996. Participants enrolled in the antibiotic group received ofloxacin 400 mg, once daily for five consecutive days, starting immediately after the procedure. Participants assigned to the control group received an identical placebo. All participants received a pictorial chart to record the amount of vaginal discharge and adverse events for two weeks after the procedure. Reported outcomes included: prevalence of prolonged vaginal discharge; postoperative vaginal bleeding requiring hospitalisation; and adverse events. From the 500 participants recruited, only 348 participants' charts were suitable for analyses (70% of total group).

Gornall 1999 was conducted in the UK. The study period was not reported. The participants allocated to the intervention group received Sultrin[®], which is antimicrobial vaginal pessary containing sulphathiazole 3.4%, sulphacetamide 2.8%, and sulphabenzamide 3.7%, twice daily for five days. Participants assigned to the control group received no treatment. All participants received patient charts to record of their symptoms and requirement of unscheduled medical visits and additional antibiotic treatment, if any during the first four weeks after the procedure. Study outcomes were: (1) severity of vaginal bleeding, discharge, and pain; and (2) the unscheduled medical visits and additional antibiotic therapy. From the 100 participants recruited, 77 participants' charts were available for analyses, corresponding to a rate of 77%.

Chan 2007 was conducted in Hong Kong between May 2003 and August 2006. Of 321 participants complying with inclusion/exclusion criteria; 157 were randomly allocated to receive antibiotics and 164 who were assigned to the control group did not receive any medication. The intervention was an antimicrobial vaginal pessary containing 100 mg tetracycline and 50 mg amphotericin B (Talsutin[®]), given twice daily for 14 days, starting on the day of large loop excision of the transformation zone (LLETZ). All participants received a diary to record the daily amount of vaginal bleeding, vaginal discharge, and lower abdominal pain for three weeks after the procedure. Study outcomes were: (1) prevalence of vaginal bleeding that required admission to hospital, additional medical consultation, additional self-medication, fever; (2) severity of vaginal bleeding, pain, and lower abdominal pain. The authors excluded 23 participants (12 in antibiotic group and 11 in

control group) because they did not return the diary. In addition, the authors excluded eight participants assigned to antibiotic group due to non-compliance with treatment, leaving 290 charts for final analyses (approximately 90% of total group).

See 'Characteristics of included studies' for full details of the included studies. Although all three included studies had been published in peer-reviewed journals at the time of the search and data extraction, numerical data regarding the outcome measured in Gornall 1999 was insufficient for meta-analyses. Attempts to obtain additional data from the investigators were not successful, since the authors did not reply to our inquiries. We therefore did not pool the results of this study and instead presented them in a narrative format.

Excluded studies

After excluding non-relevant and duplicated records, we retrieved six possibly eligible studies for more detailed evaluation. Of the six potentially eligible studies that we assessed in full-text format, we excluded three references for the following reasons (see 'Characteristics of excluded studies'). One trial was excluded because it was a non-randomised study. In addition, the treatment used in this study was cervical ablation, rather than excision, so it did not meet the review inclusion criteria (Minorchio 1990). Another reference was a randomised study evaluating effectiveness and safety of two preparations of vaginal antiseptic suppositories after cervical ablation using CO2 laser, thus it did not comply to the review inclusion criteria (Gerli 2012). The third was a randomised study, but it was excluded because the intervention that was evaluated in this study was a Monsel's solution, rather than prophylactic antibiotics (Doyle 1992).

Risk of bias in included studies

Allocation

In two included studies (Chan 2007; Foden-Shroff 1998), the participants were randomly allocated to the comparison groups with adequate allocation concealment. We therefore determined both trials as having low risk of bias. The other included study (Gornall 1999) used sealed envelopes for treatment allocation, but no details of randomisation were given. We determined this to indicate unclear risk of bias for random sequence generation and low risk of bias for allocation concealment (Figure 2).

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chan 2007							
Foden-Shroff 1998							
Gornall 1999							

Blinding

In [Foden-Shroff 1998](#), the authors provided the study medications containing either antibiotics or placebo with the same appearance and packaging. We determined this to indicate low risk of bias. In the remaining two included studies ([Chan 2007](#); [Gornall 1999](#)), participants assigned to the control group did not have a placebo control, so they were aware about the treatment allocated. We therefore judged both trials as having high risk of bias ([Figure 2](#)).

Incomplete outcome data

In the studies of [Foden-Shroff 1998](#) and [Gornall 1999](#) the rates of incomplete data were high (30% and 23%, respectively). Therefore we judged both studies as having high risk of bias. In [Chan 2007](#) 90% of participants had complete data, indicating low risk of bias ([Figure 2](#)).

Selective reporting

Although the study protocols of included studies were not available ([Chan 2007](#); [Foden-Shroff 1998](#); [Gornall 1999](#)), the authors did report the expected relevant outcomes, so we judged this domain to be at a low risk of bias ([Figure 2](#)).

Other potential sources of bias

The analyses performed in all three included studies ([Chan 2007](#); [Foden-Shroff 1998](#); [Gornall 1999](#)) did not follow an intention-to-treat basis. Additionally, in [Gornall 1999](#), there were no data regarding the review inclusion and exclusion criteria applied. The authors also did not provide the data regarding the baseline characteristics of participants and number of participants allocated to each comparison group, which are mandatory for determining treatment outcomes and assessing the quality of study methodology. So, we deemed this domain to have a high risk of bias ([Figure 2](#)).

Effects of interventions

See: [Summary of findings for the main comparison](#)

See: [Differences between protocol and review](#)

Primary outcomes

Infectious complications

Prolonged vaginal discharge

Only [Foden-Shroff 1998](#) reported the incidence of prolonged vaginal discharge after cervical excision in the two comparison groups. Participants receiving prophylactic antibiotics had a higher incidence of prolonged vaginal discharge after LLETZ compared to those who were assigned to placebo group (13.3% versus 10.3%, respectively; [Table 1](#)). However, there was no statistical difference (one study; 348 participants; risk ratio (RR), 1.29; 95% confidence interval (CI) 0.72 to 2.31; low-quality evidence). See [Summary of findings for the main comparison](#); [Analysis 1.1](#).

Severe vaginal bleeding

All included studies reported the incidence of severe vaginal bleeding requiring hospital admission. However, numerical data regarding this outcome measured in the study [Gornall 1999](#) was insufficient for meta-analyses. In [Foden-Shroff 1998](#), only 1.2% of participants assigned to the antibiotic group experienced severe vaginal bleeding requiring hospitalisation, which was comparable to the 1.7% reported for participants in the placebo group ([Table 1](#)). In [Chan 2007](#), participants receiving prophylactic antibiotics had a higher incidence of severe vaginal bleeding requiring hospitalisation compared to those who were assigned to placebo group (6.6% versus 4.6%, respectively; [Table 1](#)). After combining data from [Foden-Shroff 1998](#) and [Chan 2007](#), there was no difference (638 participants; RR 1.21; 95% CI 0.52 to 2.82; very low-quality evidence). See [Summary of findings for the main comparison](#); [Analysis 2.1](#).

In [Gornall 1999](#), of the 77 participants, two assigned to the control group were admitted because of excessive vaginal bleeding. None of the participants who received antibiotics had severe vaginal bleeding ([Table 2](#)).

Fever

Only [Chan 2007](#) reported the incidence of fever following excision of the cervical transformation zone and demonstrated no difference between the groups (one study; 290 participants; RR, 2.23; 95% CI 0.20 to 24.36; very low-quality of evidence). See [Summary of findings for the main comparison](#); [Analysis 3.1](#).

Lower abdominal pain

The incidence of postoperative lower abdominal pain was reported in one of three included studies ([Chan 2007](#)). Approximately 16.8% of participants assigned to the antibiotic group experienced lower abdominal pain following LLETZ, which was comparable to the 16.3% reported for participants in the control group ([Table 1](#)) (one study; 290 participants; RR, 1.03; 95% CI 0.61 to 1.72; low-quality evidence). See [Summary of findings for the main comparison](#); [Analysis 4.1](#).

Additional antibiotic treatment

Gornall 1999 reported that, of 77 participants available for the study analyses, two and seven participants assigned to the antibiotic and control group, respectively, received additional antibiotics. Because of missing data regarding the number of participants in each comparison group, the incidence of the requirement of additional antibiotic treatment among the two comparison groups and the relative effect of prophylactic antibiotics, could not be determined (Table 2). Foden-Shroff 1998 and Chan 2007 did not report the requirement of additional antibiotic treatment in their studies.

Other infectious complications

The included studies did not report the incidence of cervicitis, endometritis, and pelvic inflammatory disease.

Antibiotic resistance

No information on antibiotic resistance was reported in any of the included studies.

Secondary outcomes

Adverse effects

No reported data on the rate of adverse events were available for Gornall 1999 (Table 2). In Chan 2007, no participants reported antibiotic adverse events (Table 1). Foden-Shroff 1998 reported that 11.6% of participants who received antibiotic experienced adverse events, including nausea, vomiting, diarrhoea, and headache, which was higher than the 6.9% reported in participants assigned to placebo group. When we pooled the data from these two included studies (Chan 2007; Foden-Shroff 1998), no difference was demonstrated (638 participants; RR 1.69; 95% CI 0.85 to 3.34; very low-quality evidence). See [Summary of findings for the main comparison: Analysis 5.1](#).

Unscheduled medical consultation

Only Chan 2007 reported the rate of unscheduled medical consultation in the two comparison groups. Participants receiving antimicrobial vaginal pessary had a higher rate of unscheduled medical consultation than those who were assigned to the control arm (8.8% versus 3.3%, respectively), but this difference was not significant (one study, 290 participants; RR 2.68, 95% CI 0.97 to 7.41; low-quality evidence). See [Summary of findings for the main comparison: Analysis 6.1](#).

Additional self-medication

The rate of additional self-medication was reported in one study (Chan 2007). Approximately 8.8% of participants assigned to antibiotic group reported to have self-medication which was comparable to the 7.2% reported for participants in the control group (one study; 290 participants; RR 1.22; 95%CI 0.56 to 2.67; very low-quality evidence; [Summary of findings for the main comparison: Analysis 7.1](#)).

DISCUSSION

Summary of main results

We found three studies that met our inclusion criteria. However, numerical data regarding the outcome measured in one small study was insufficient for inclusion in the meta-analyses. Evidence from this review indicates that there were no differences between women receiving prophylactic antibiotics and those receiving a placebo or no treatment in terms of prolonged vaginal discharge, severe vaginal bleeding, fever, lower abdominal pain, requirement of unscheduled medical consultation, and self-medication. In addition, the number of adverse events did not differ between the two comparison groups. None of the three included studies reported data on antibiotic resistance. However, it is unknown whether these symptoms were due to infection, since samples for microbiological culture were not routinely taken in these studies and symptoms were largely self-reported.

Overall completeness and applicability of evidence

This review included three randomised controlled trials (RCTs) evaluating prophylactic antibiotic in 708 participants who had undergone large loop excision of the transformation zone (LLETZ) procedure in the UK and Hong Kong. The interventions evaluated in the included studies were different antibiotic regimens to prevent infection following excision of the cervical transformation zone. Primary outcomes of this review were signs and symptoms suggesting infectious complications including: cervicitis; endometritis; pelvic inflammatory disease; prolonged vaginal discharge; severe vaginal bleeding; lower abdominal pain; fever; and additional antibiotic treatment received. Secondary outcomes included adverse events; antibiotic resistance; and incidence of unscheduled medical consultation and self-medication. However, the included studies did not report the incidence of cervicitis, endometritis, pelvic inflammatory disease, and antibiotic resistance. It is important to note that the excisional method used in all three included studies was LLETZ. Therefore, the same results may not be applicable to other excisional techniques. In addition, the two

studies included in the review that tested drugs targeting *Chlamydia trachomatis* took place in a population with a prevalence of chlamydial infection that varied from 2% to 10% (Chan 2007; Foden-Shroff 1998). The other antimicrobial used was vaginal pessary, which was a preparation used against *Haemophilus (Gardnerella) vaginalis* (Gornall 1999). Therefore, generalisation of the results to different settings and different antibiotics or a combination of antibiotics may be limited.

Quality of the evidence

The greatest threat to the validity of the included study is likely to be the risk of bias (see Figure 2). In all included studies, treatment outcomes were measured using self-reported data from participants. However, participants assigned to the control groups of two included studies did not receive a placebo. Thus, these participants were unblinded for treatment allocated, resulting in a high risk of performance and detection biases (Chan 2007; Gornall 1999). Another limitation for this review was the potential risk of attrition bias. Lack of data for final analyses were considerable, greater than 20% in two included studies (Foden-Shroff 1998; Gornall 1999). In addition, analyses carried out in all included studies did not follow an intention-to-treat principle. Data from one study involving 77 participants were also limited. The authors of this study did not provide additional information. Baseline characteristics of participants, and number of participants allocated to each comparison group, which are necessary for assessing the effects of treatment and quality of study methodology, were not available (Gornall 1999).

Another major limitation of this review is the small number of included studies, which has the potential to affect the accuracy in determining statistical heterogeneity and thus we used random-effects model for all meta-analyses.

We assessed the quality of evidence using the GRADE approach for each outcome (see Summary of findings for the main comparison). Based on the concerns regarding the risk of the potential bias, we downgraded the evidence to low quality for the incidences of prolonged vaginal discharge, lower abdominal pain, unscheduled medical consultant, and self-medication. We downgraded the evidence to very low quality for severe vaginal bleeding, postoperative fever, and adverse events due to the potential biases and sparseness of data. We found no available evidence on the potential risk of antibiotic resistance, one of the most serious health threats, following the use of antibiotic prophylaxis for excision of the cervical transformation zone.

Potential biases in the review process

With assistance from the Information Specialist, Cochrane Gynaecological, Neuro-oncology & Orphan Cancer Group, we made every attempt to include global studies including a thorough search

of the grey literature, conference proceedings, and ongoing trials. However, as there were only three studies that met the review inclusion criteria, there remains the possibility that there may be other unpublished trials of intervention that the review authors did not discover. This means that the review authors may unwittingly have perpetuated a publication bias. Another source of potential biases is our inability to obtain relevant incomplete data leading to the exclusion of one small study (Gornall 1999) from the meta-analysis.

None of the review authors have any links to drug companies or a financial interest in the prescription of the drug under assessment, nor were they involved in the conduct of the included study. Thus, there were no issues associated to bias secondary to conflicts of interests in this review.

Agreements and disagreements with other studies or reviews

According to the surgical wound classification system, an excision of the cervical transformation zone is considered as a clean-contaminated procedure. Although ACOG (ACOG 2009) and the National Institute for Health and Care Excellence (NICE 2008) generally recommend prophylactic antibiotics for clean-contaminated procedures, findings from this review show that there is not sufficient evidence to support routine antibiotics for infection prevention after LLETZ procedure. This conclusion is in broad agreement with previously published reviews (Craciunas 2014; Morrill 2013).

Antibiotic resistance is one of the biggest threats to global health and requires urgent, co-ordinated action across all healthcare sectors (Del Mar 2012; WHO 2015). The misuse of antibiotics accelerates the emergence of drug-resistant bacteria (WHO 2015). As noted in previous reports in a variety of clinical settings, administration of antibiotic prophylaxis can be a risk factor for antibiotic resistance (Bitsori 2014; McMurray 2015; Minami 2014). Therefore, the potential benefits and possible harms of prophylactic antibiotics should be carefully assessed and considered, particularly for the risk of developing antibiotic resistance. However, there has been little discussion of potential risk of antibiotic resistance after administration of prophylactic antibiotics in previous reports (Buppasiri 2014; Grimes 1999; Morrill 2013; Sawaya 1996). In this review, none of the included studies reported data on antibiotic resistance.

AUTHORS' CONCLUSIONS

Implications for practice

The limited evidence obtained from the three randomised controlled trials (RCTs) presented in this review found no benefit

of antibiotics given to prevent infection following excision of the cervical transformation zone for cervical neoplasia. In addition, evidence for the safety of antibiotics used in this surgical setting is inconclusive, due to a small number of reported adverse events, incomplete data available for analyses, and lack of information on antibiotic resistance. The evidence does not support the routine administration of prophylactic antibiotics in women undergoing excision of the cervical transformation zone. At the present, antibiotics given for infection prevention after excision of the cervical transformation zone should be limited to appropriately conducted clinical research.

Implications for research

The effectiveness and safety of antibiotics for infection prevention following excision of the cervical transformation zone were inadequately assessed in the included studies according to an intention-to-treat basis. Additionally, the trials in all of the comparisons were at high or moderate risk of bias, so the quality of the evidence was low or very low for these outcomes across all comparisons. Further research therefore is likely to have an important impact on our confidence in the estimates of effect and may alter the estimates in the treatment comparisons. However, this would be dependent

on the studies being of high quality, adequately sized, placebo-controlled, with a well-defined protocol for appropriate outcomes measured and statistical analyses to delineate the effectiveness and safety of antibiotics. Any studies should include an assessment on the effect of antibiotic resistance.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Chan 2007

Methods	A randomised-controlled trial conducted in the colposcopy clinic at Queen Mary Hospital, University of Hong Kong Study duration: May 2003 to August 2006.	
Participants	All women who attended the clinic for LLETZ. Exclusion criteria: history of antibiotic hypersensitivity, liver or renal disease, previous psychiatric problems or receiving antibiotics within the 2 weeks prior to the visit. All participants receive a diary to record the daily amount of vaginal bleeding, vaginal discharge, and lower abdominal pain for 3 weeks after the procedure Of 321 participants complying with inclusion/exclusion criteria; 157 were randomly allocated to receive antibiotics and 164 did not receive any medications Mean age of participants in antibiotic and those in control groups were 38.4 years and 40.5 years, respectively. Approximately 57.7% and 61.4% of participants assigned to antibiotic and control groups, respectively, had positive endocervical swabs. Approximately 27.0% and 34.8% of participants assigned to antibiotic and control groups, respectively, had positive high vaginal swabs. Approximately 4.4% and 2.0% of participants assigned to antibiotic and control groups, respectively, had positive test for <i>Chlamydia</i>. Weight of excised specimens obtained among the participants allocated to antibiotic and control groups, respectively, was 2.2 g and 1.9 g. Approximately 67.2% and 63.4% of participants assigned to antibiotic and control groups, respectively, had high-grade lesion on conization specimens	
Interventions	Antimicrobial vaginal pessary containing 100 mg tetracycline and 50 mg amphotericin B (Talsutin [®] , Bristol-Myers Squibb New York, NY, USA) two times a day for 14 days, starting on the day of LLETZ. The control group did not receive any medications. Tetracycline is mainly an anti-chlamydial agent. Amphotericin B is an antifungal antibiotic	
Outcomes	The primary outcome was the incidence of post-LLETZ bleeding that required medical attention The secondary outcomes were the severity of postoperative vaginal bleeding, vaginal discharge, and lower abdominal pain in the 3 weeks after the procedure recorded in the participants' diary. All participants were assessed about the complications at 3 weeks after LLETZ	
Notes	The authors excluded 23 participants (12 in antibiotic group and 11 in control group) because they did not return the diary. In addition, the authors excluded 8 participants assigned to antibiotic group because of incomplete the course of treatment prescribed, leaving 290 charts for final analyses (approximately 90% of total group). Therefore, the analyses performed in this study did not follow an intention-to-treat basis	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	This trial used block randomisation with a randomised size of four. This study declared that "generation of randomisation schedule was performed by a person independent of the recruitment, and the seed from which the randomisation schedule was generated was kept securely by the randomiser."
Allocation concealment (selection bias)	Low risk	A quote from the study: "Sealed opaque envelopes containing the randomised treatment allocation was prepared and kept by the research assistant prior to the start of patient recruitment"
Blinding of participants and personnel (performance bias) All outcomes	High risk	A quote from the study: "The result of the randomisation was blinded to the research assistant but not to the colposcopist who needed to prescribe the medication for the treatment group at the clinic immediately after the procedure". In addition, the authors did not use placebo for the participant assigned to the control group so the participants were not blinded to treatment allocated."
Blinding of outcome assessment (detection bias) All outcomes	High risk	The study outcomes were based on the participants' self-assessment on their symptoms after the procedure. As participants were aware about the treatment received, there is high risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Twenty-three participants did not return the diary (7.2%).
Selective reporting (reporting bias)	Low risk	All potential relevant outcomes were reported.
Other bias	High risk	This study excluded 23 participants due to not return their diary (12 in antibiotic group and 11 in control group) and 8 participants in the treatment group from the final analyses because of incomplete the course of treatment. So, the analyses performed in this study was not based on intention-to-treat

Foden-Shroff 1998

Methods	A randomised double-blind, placebo-controlled study conducted in a large teaching hospital colposcopy clinic in UK Study duration: July 1994 to August 1996
Participants	The participants were women aged between 20 and 65 undergoing loop diathermy excision. Exclusion criteria: a history of antibiotic hypersensitivity, renal or hepatic diseases, previous psychiatric problems, and receiving antibiotic within the preceding 14 days. All participants received pictorial chart to record the amount of vaginal loss and adverse events for 2 weeks after the procedure. The participants had to return their chart in a stamped addressed envelopes which were provided by the trial authors Of 500 participants complying with inclusion/exclusion criteria; 250 were randomly allocated to receive antibiotics and 250 to receive placebo. The mean ages for the participants in antibiotic and placebo groups were 37.0 and 37.1 years, respectively. Approximately 60.4% and 53.6% of participants assigned to antibiotic and control groups, respectively, had underlying high-grade cervical lesion on excised specimens. Approximately 32.8% and 28.8% of participants enrolled to antibiotic and control groups, respectively, underwent multiple passes of loop excision. 418 participants (70%) returned pictorial chart, but 70 were subsequently excluded due to incomplete data, leaving 348 charts (173 in the antibiotic group and 175 in the placebo group) for final analyses
Interventions	Participants enrolled in the antibiotic group received ofloxacin 400 mg (2 x 200 mg) once daily for five consecutive days, starting immediately after the procedure. Participants assigned to the control group received identical placebo given in the same fashion. Ofloxacin is antimicrobial antibiotics with special activity against Chlamydial infections
Outcomes	The amount of postoperative vaginal discharge estimated by participants' self assessment using pictorial chart
Notes	Of 500 participants recruited, only 348 participants' charts were eligible for study analyses, corresponding to a rate of approximately 70% The authors stated that the prevalence of Chlamydial infections among their colposcopy population was 10%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A quote from the study: "the study medication had been randomly assigned to the patient numbers in advance by the manufacture on a 1:1 basis"
Allocation concealment (selection bias)	Low risk	Following the procedure, participants were allocated their study number and received the study medication carrying her number
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Investigators and participants involving in this trial were blinded to the treatment received. Patients received either antibiotic or

Foden-Shroff 1998 (Continued)

		identical placebo, which had been prepared in the same packaging
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study outcome was the participants' self-assessment on postoperative vaginal loss using pictorial charts. As the participants were blinded about the treatment received, there is low risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	High risk	Of 500 participants enrolled, adequate information for study analyses were obtained from only 348 participants
Selective reporting (reporting bias)	Low risk	All potential relevant outcomes were reported.
Other bias	High risk	This study excluded participants who did not return their charts and those with inadequate information on their charts. Thus, the analyses performed did not follow an intention-to-treat basis

Gornall 1999

Methods	A randomised-controlled trial conducted in the colposcopy clinic at the Princess Anne Hospital, Southampton, UK Study duration: not reported
Participants	The participants were women undergoing LLETZ. The trial authors did not stated exclusion criteria. All participants received patients' charts contained a daily record of vaginal bleeding, vaginal discharge, and pain for 4 weeks after the procedure. The participants were asked to record the requirement of unscheduled medical visits and additional antibiotic treatment, if any. The participants had to return their chart at 3 months following the procedure. Initially, this study recruited 100 participants but only 77 returned their charts for analyses
Interventions	Participants allocated to the intervention group received Sultrin which is antimicrobial vaginal pessary containing sulphathiazole 3.42%, sulphacetamide 2.86%, and sulphabenzamide 3.7%, twice daily for 5 days. Participants assigned as the control group received no treatment. Sultrin vaginal pessary is a preparation used intravaginally against <i>Haemophilus (Garnerella) vaginalis</i> .
Outcomes	- Severity of vaginal bleeding, discharge, and pain during the initial 28 days after the procedure which were assessed by a numerical score from 1 to 3 - The requirements of unscheduled medical visits and additional antibiotic therapy
Notes	The authors did not reported the details regarding the processes of randomisation and treatment allocation. In addition, of 100 participants recruited, only 77 participants'

	charts were available for analyses, corresponding to a rate of 77%.The authors did not reported the baseline characteristics of the participants, treatment-related events, and actual number of participants assigned in each comparison group	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The authors did not reported the details of the processes of randomisation
Allocation concealment (selection bias)	Low risk	The authors used sealed envelope during randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	The authors did not use placebo for the participant assigned to the control group so the participants were not blinded to treatment received
Blinding of outcome assessment (detection bias) All outcomes	High risk	Because the outcome based on the participants’ self-assessment on their symptoms occurring after the procedure but the participants were aware about the treatment received
Incomplete outcome data (attrition bias) All outcomes	High risk	of 100 participants recruited, only 77 participants’ charts were available for analyses, corresponding to a rate of incomplete outcome data of approximately 23%
Selective reporting (reporting bias)	Low risk	All potential relevant outcomes were reported.
Other bias	High risk	This study excluded participants who did not return their charts. Therefore, the analyses carried out in this study was not based on an intention-to-treat The authors did not state about the review inclusion and exclusion criteria applied in this study. The authors also did not report the baseline characteristics of participants and number of participants allocated to each comparison group which are mandatory for determining treatment outcomes and assessing the quality of study methodology

LLETZ: large loop excision of the transformation zone

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Doyle 1992	This randomised study was excluded because the intervention used was a Monsel's solution applied after cervical excision which was not a prophylactic antibiotics, the intervention that this review aims to address
Gerli 2012	This randomised study entitled " <i>Antiseptic regimen in the surgical treatment of HPV generated cervical lesions: polyhexamethylene biguanide vs chlorhexidine. A randomised, double blind study</i> " was conducted to determine the effectiveness and safety of polyhexamethylene biguanide-based vaginal suppositories compared to chlorhexidine-based preparation. However, the treatment used in this study was an ablation using CO2 laser which did not meet our review inclusion
Minorchio 1990	This study entitled " <i>Advantages of topical therapy with polydeoxyribonucleotide in reparative processes after cauterization: Experience at a centre for early diagnosis of genital neoplasm</i> " was conducted to evaluate the effectiveness of kanamycin sulphate alternated with placebo versus polydeoxyribonucleotide vaginal suppositories for preventing postoperative infection and promoting tissue healing after cauterisation of the uterine cervix. However, this study was a controlled clinical trial and the treatment used in this study was not an excisional method

DATA AND ANALYSES

Comparison 1. Prolonged vaginal discharge

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants who experienced prolonged vaginal discharge	1	348	Risk Ratio (IV, Random, 95% CI)	1.29 [0.72, 2.31]

Comparison 2. Excessive vaginal bleeding

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants who had to be admitted for postoperative bleeding	2	638	Risk Ratio (IV, Random, 95% CI)	1.21 [0.52, 2.82]

Comparison 3. Fever

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants who developed fever	1	290	Risk Ratio (IV, Random, 95% CI)	2.23 [0.20, 24.36]

Comparison 4. Lower abdominal pain

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants who experienced lower abdominal pain	1	290	Risk Ratio (IV, Random, 95% CI)	1.03 [0.61, 1.72]

Comparison 5. Adverse effects

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants who experienced any adverse effects related to antibiotics	2	638	Risk Ratio (IV, Random, 95% CI)	1.69 [0.85, 3.34]

Comparison 6. Unscheduled medical consultant

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants who received additional medical consultant (for any reasons)	1	290	Risk Ratio (IV, Random, 95% CI)	2.68 [0.97, 7.41]

Comparison 7. Additional self-medication

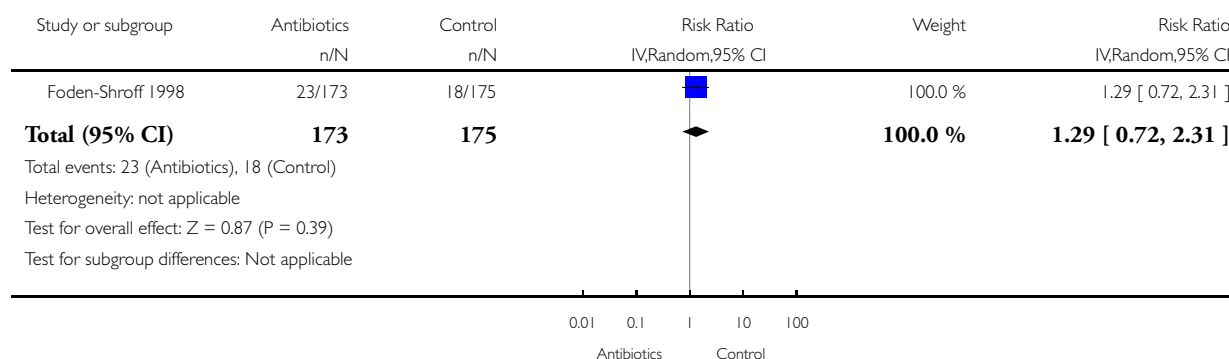
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants who had additional self-medication	1	290	Risk Ratio (IV, Random, 95% CI)	1.22 [0.56, 2.67]

Analysis 1.1. Comparison 1 Prolonged vaginal discharge, Outcome 1 Number of participants who experienced prolonged vaginal discharge.

Review: Antibiotics for infection prevention after excision of the cervical transformation zone

Comparison: 1 Prolonged vaginal discharge

Outcome: 1 Number of participants who experienced prolonged vaginal discharge

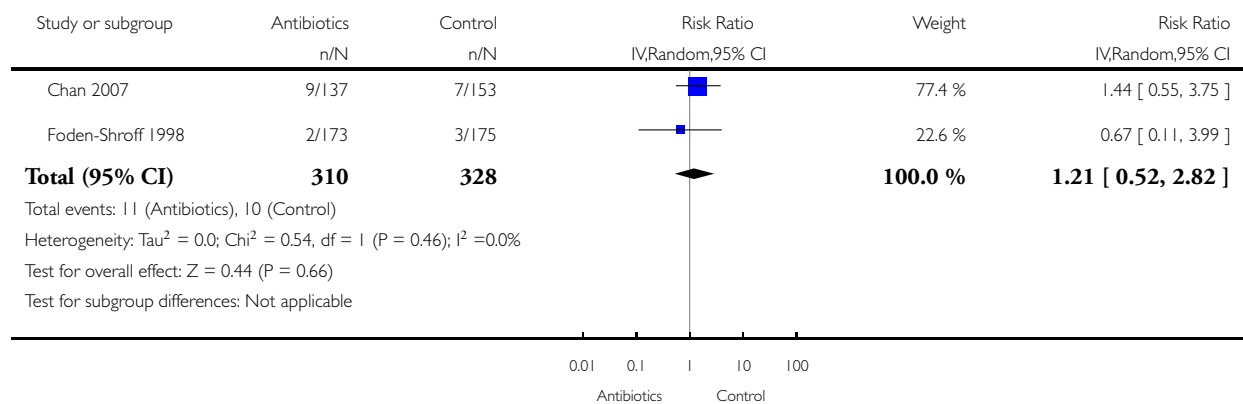


Analysis 2.1. Comparison 2 Excessive vaginal bleeding, Outcome 1 Number of participants who had to be admitted for postoperative bleeding.

Review: Antibiotics for infection prevention after excision of the cervical transformation zone

Comparison: 2 Excessive vaginal bleeding

Outcome: 1 Number of participants who had to be admitted for postoperative bleeding

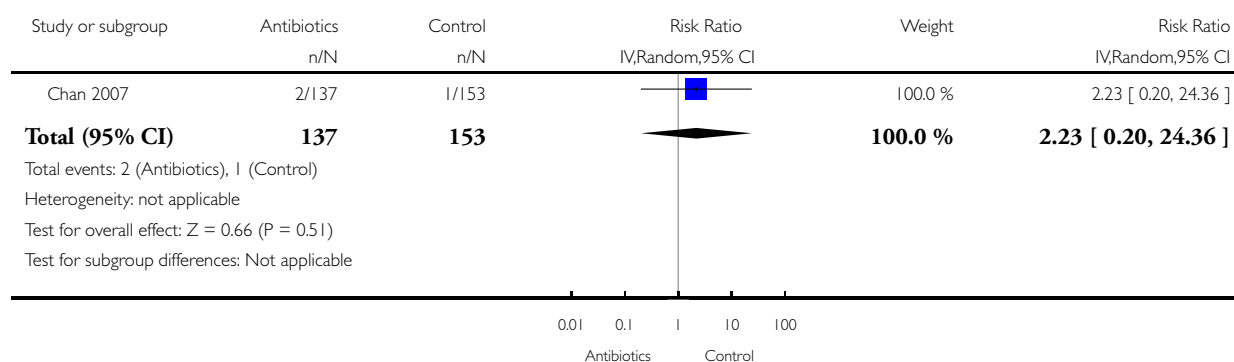


Analysis 3.1. Comparison 3 Fever, Outcome 1 Number of participants who developed fever.

Review: Antibiotics for infection prevention after excision of the cervical transformation zone

Comparison: 3 Fever

Outcome: 1 Number of participants who developed fever

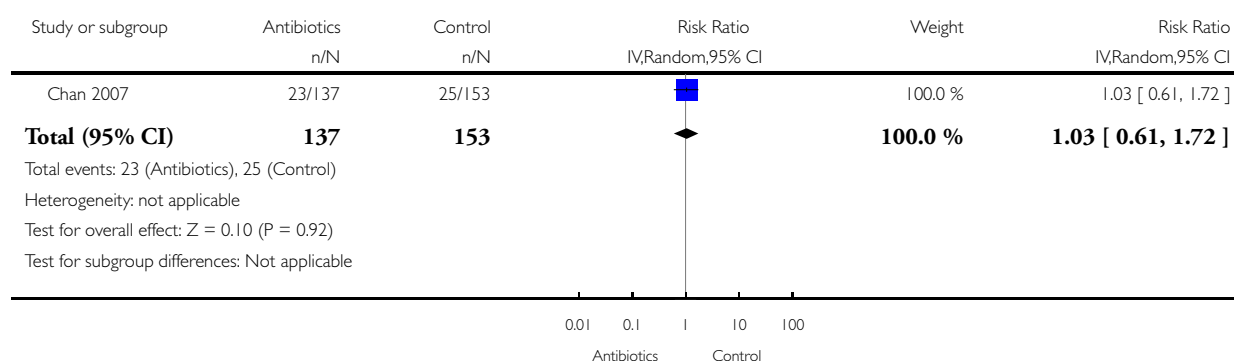


Analysis 4.1. Comparison 4 Lower abdominal pain, Outcome 1 Number of participants who experienced lower abdominal pain.

Review: Antibiotics for infection prevention after excision of the cervical transformation zone

Comparison: 4 Lower abdominal pain

Outcome: 1 Number of participants who experienced lower abdominal pain

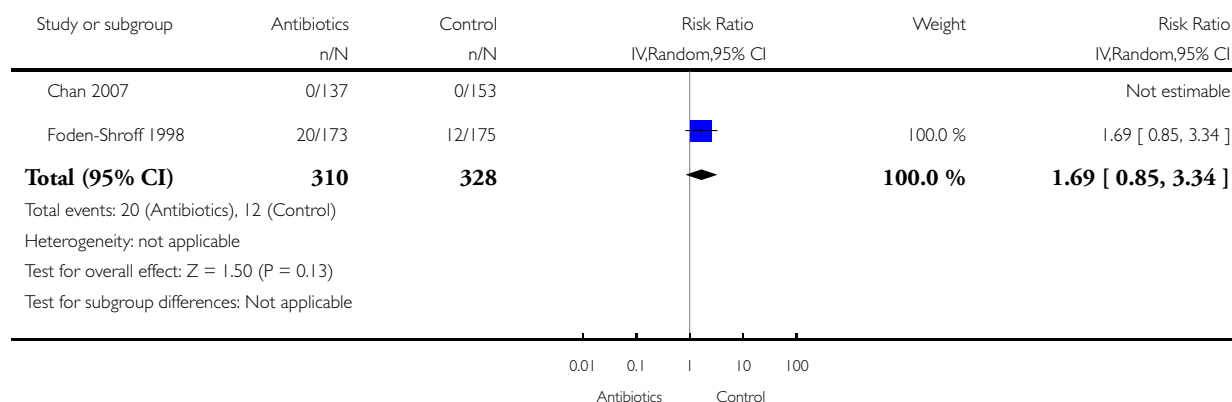


Analysis 5.1. Comparison 5 Adverse effects, Outcome 1 Number of participants who experienced any adverse effects related to antibiotics.

Review: Antibiotics for infection prevention after excision of the cervical transformation zone

Comparison: 5 Adverse effects

Outcome: 1 Number of participants who experienced any adverse effects related to antibiotics

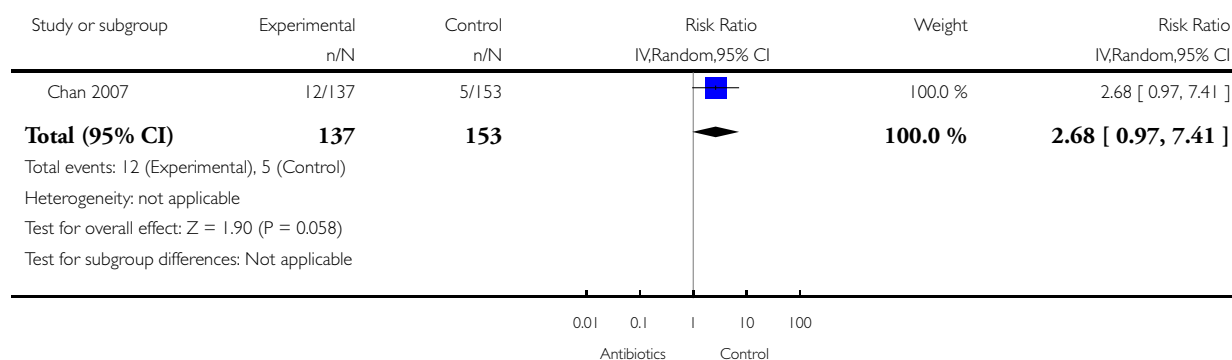


Analysis 6.1. Comparison 6 Unscheduled medical consultant, Outcome 1 Number of participants who received additional medical consultant (for any reasons).

Review: Antibiotics for infection prevention after excision of the cervical transformation zone

Comparison: 6 Unscheduled medical consultant

Outcome: 1 Number of participants who received additional medical consultant (for any reasons)

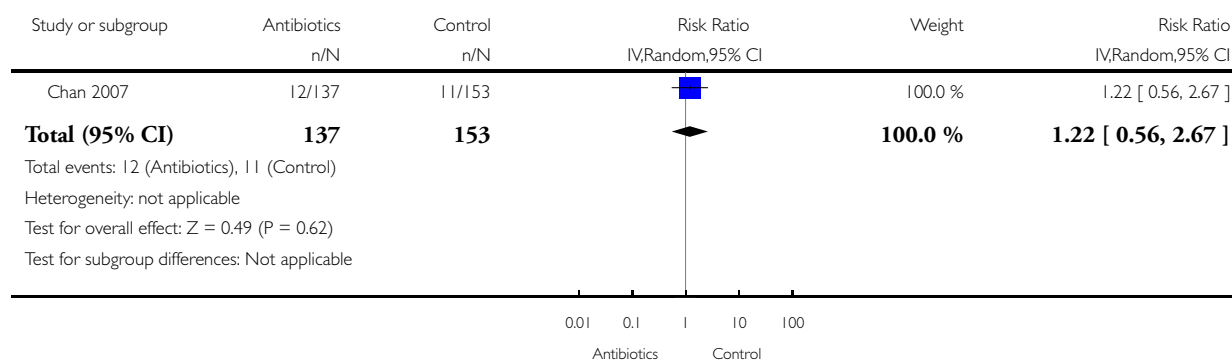


Analysis 7.1. Comparison 7 Additional self-medication, Outcome 1 Number of participants who had additional self-medication.

Review: Antibiotics for infection prevention after excision of the cervical transformation zone

Comparison: 7 Additional self-medication

Outcome: 1 Number of participants who had additional self-medication



ADDITIONAL TABLES

Table 1. Extracted data from Chan 2007 and Foden-Shroff 1998

Study	Antibiotic group	Placebo or no treatment
Number of participants who experienced prolonged vaginal discharge		
Foden-Shroff 1998	23/173 (13.3%)	18/175 (10.3%)
Number of participants who had to be admitted for post-procedure bleeding		
Foden-Shroff 1998	2/173 (1.2%)	3/175 (1.7%)
Chan 2007	9/137 (6.6%)	7/153 (4.6%)
Number of participants who experienced lower abdominal pain		
Chan 2007	23/137 (16.8%%)	25/153 (16.3%)
Number of participants who developed fever		

Table 1. Extracted data from Chan 2007 and Foden-Shroff 1998 (Continued)

Chan 2007	2/137 (1.5%)	1/153 (0.7%)
Number of participants who experienced adverse events		
Foden-Shroff 1998	20/173 (11.6%)	12/175 (6.9%)
Chan 2007	0/137 (0%)	0/153 (0%)
Number of participants who required unscheduled medical consultation		
Chan 2007	12/137 (8.8%)	5/153 (3.3%)
Number of participants reported to have additional self-medication		
Chan 2007	12/137 (8.8%)	11/153 (7.2%)

Table 2. Reported data from Gornall 1999

Outcomes reported in Gornall 1999	Sultrin (sample size = n)	Control (sample size = 77-n)	95% confidence interval	P value
Mean duration of bleeding (days)	15.2	11.2	-7.7 to -0.2	0.04
Mean duration of discharge (days)	16.4	13.1	-7.2 to 0.7	0.11
Mean duration of pain (days)	7.7	5.7	-5.4 to 1.5	0.26
Number of participants who received additional antibiotic therapy	2	7	Not reported	Not reported
Number of participants who had to be admitted for postoperative bleeding	0	2	Not reported	Not reported

Numbers of the participant in each comparison group were not reported.

APPENDICES

Appendix 1. CENTRAL search strategy

- #1 MeSH descriptor Antibiotic Prophylaxis, this term only
- #2 MeSH descriptor Anti-Infective Agents, this term only
- #3 MeSH descriptor Cephalosporins explode all trees
- #4 MeSH descriptor Penicillins explode all trees
- #5 MeSH descriptor Macrolides explode all trees
- #6 MeSH descriptor Fluoroquinolones explode all trees
- #7 MeSH descriptor Sulfonamides explode all trees
- #8 MeSH descriptor Tetracyclines explode all trees
- #9 MeSH descriptor Aminoglycosides explode all trees
- #10 MeSH descriptor Glycopeptides explode all trees
- #11 MeSH descriptor Antiprotozoal Agents explode all trees
- #12 (antibiotic* or antimicrob* or anti-microb* or antibacteria* or anti-bacteria* or antiinfect* or anti-infect*)
- #13 ((prevent* or prophyla*) near/5 (bacteria* or microb* or infect*))
- #14 (cef* or ceph* or loracarbef* or penicillin* or amoxicillin or erythromycin or clarithromycin or azithromycin or metronidazole or ciprofloxacin or levofloxacin or ofloxacin or co-trimoxazole or cotrimoxazole or trimethoprim or tetracycline or doxycycline or gentamycin or gentamicin or vancomycin or augmentin)
- #15 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)
- #16 MeSH descriptor Uterine Cervical Neoplasms, this term only
- #17 MeSH descriptor Cervical Intraepithelial Neoplasia, this term only
- #18 MeSH descriptor Cervix Uteri, this term only
- #19 cervi*
- #20 (#16 OR #17 OR #18 OR #19)
- #21 Any MeSH descriptor with qualifier: SU
- #22 (surg* or excis* or laser* or conization)
- #23 MeSH descriptor Gynecologic Surgical Procedures explode all trees
- #24 (LEEP or LLETZ or LC or CKC)
- #25 (#21 OR #22 OR #23 OR #24)
- #26 (#15 AND #20 AND #25)

Appendix 2. MEDLINE search strategy

Medline (Ovid)

- 1 Antibiotic Prophylaxis/
- 2 exp Anti-Infective Agents/
- 3 exp Cephalosporins/
- 4 exp Penicillins/
- 5 exp Macrolides/
- 6 exp Fluoroquinolones/
- 7 exp Sulfonamides/
- 8 exp Tetracyclines/
- 9 exp Aminoglycosides/
- 10 exp Glycopeptides/
- 11 exp Antiprotozoal Agents/
- 12 (antibiotic* or antimicrob* or anti-microb* or antibacteria* or anti-bacteria* or antiinfect* or anti-infect*).mp.
- 13 ((prevent* or prophyla*) adj5 (bacteria* or microb* or infect*)).mp.
- 14 (cef* or ceph* or loracarbef* or penicillin* or amoxicillin or erythromycin or clarithromycin or azithromycin or metronidazole or ciprofloxacin or levofloxacin or ofloxacin or co-trimoxazole or cotrimoxazole or trimethoprim or tetracycline or doxycycline or gentamycin or gentamicin or vancomycin or augmentin).mp.
- 15 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14

16 Uterine Cervical Neoplasms/
 17 Cervical Intraepithelial Neoplasia/
 18 Cervix Uteri/
 19 cervi*.mp.
 20 16 or 17 or 18 or 19
 21 surgery.fs.
 22 (surg* or excis* or laser* or conization).mp.
 23 exp Gynecologic Surgical Procedures/
 24 (LEEP or LLETZ or LC or CKC).mp.
 25 21 or 22 or 23 or 24
 26 15 and 20 and 25
 27 randomized controlled trial.pt.
 28 controlled clinical trial.pt.
 29 randomized.ab.
 30 placebo.ab.
 31 drug therapy.fs.
 32 randomly.ab.
 33 trial.ab.
 34 groups.ab.
 35 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
 36 26 and 35
 37 exp animals/ not humans.sh.
 38 36 not 37
 key:
 mp=title, original title, abstract, name of substance word, subject heading word, unique identifier
 pt=publication type
 fs=floating subheading
 sh=subject heading

Appendix 3. Embase search strategy

Embase (Ovid)
 1 antibiotic prophylaxis/
 2 exp antiinfective agent/
 3 exp cephalosporin derivative/
 4 exp penicillin derivative/
 5 exp macrolide/
 6 exp quinolone derivative/
 7 exp sulfonamide/
 8 exp tetracycline derivative/
 9 exp aminoglycoside/
 10 exp glycopeptide/
 11 exp antiprotozoal agent/
 12 (antibiotic* or antimicrob* or anti-microb* or antibacteria* or anti-bacteria* or antiinfect* or anti-infect*).mp.
 13 ((prevent* or prophyla*) adj5 (bacteria* or microb* or infect*)).mp.
 14 (cef* or ceph* or loracarbef* or penicillin* or amoxicillin or erythromycin or clarithromycin or azithromycin or metronidazole or ciprofloxacin or levofloxacin or ofloxacin or co-trimoxazole or cotrimoxazole or trimethoprim or tetracycline or doxycycline or gentamycin or gentamicin or vancomycin or augmentin).mp.
 15 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
 16 exp uterine cervix tumor/
 17 uterine cervix carcinoma in situ/
 18 exp uterine cervix/

19 cervi*.mp.
 20 16 or 17 or 18 or 19
 21 su.fs.
 22 (surg* or excis* or laser* or conization).mp.
 23 exp gynecologic surgery/
 24 (LEEP or LLETZ or LC or CKC).mp.
 25 21 or 22 or 23 or 24
 26 15 and 20 and 25
 27 crossover procedure/
 28 double-blind procedure/
 29 randomized controlled trial/
 30 single-blind procedure/
 31 random*.mp.
 32 factorial*.mp.
 33 (crossover* or cross over* or cross-over*).mp.
 34 placebo*.mp.
 35 (double* adj blind*).mp.
 36 (singl* adj blind*).mp.
 37 assign*.mp.
 38 allocat*.mp.
 39 volunteer*.mp.
 40 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
 41 26 and 40
 42 (exp Animal/ or Nonhuman/ or exp Animal Experiment/) not Human/
 43 41 not 42

key:

[mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

Appendix 4. LILACS search strategy

1 Antibiotic OR Anti-bacterial agents/
 2 cephalosporins
 3 penicillins
 4 macrolides
 5 fluoroquinolones
 6 sulfonamides
 7 aminoglycosides
 8 glycopeptides
 9 antiprotozoals
 10 erythromycin
 11 clarithromycin
 12 metronidazole
 13 azithromycin
 14 methronidazole
 15 ciprofloxacin
 16 levofloxacin
 17 ofloxacin
 18 trimethoprim
 19 tetracycline
 20 doxycycline
 21 vancomycin

22 augmentin
 23 #1 or # 2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22
 24 infection or prevention
 25 cervical intraepithelial surgery or cervix uteri surgery
 26 randomized or clinical trials or controlled or trial
 27 #23 and #24 and #25 and #26

Appendix 5. 'Risk of bias' assessment

Risk of bias assessment based on chapter 8 of [Higgins 2011](#);

- Random sequence generation
 - i) Low risk of bias e.g. participants assigned to treatments on the basis of a computer-generated random sequence or a table of random numbers
 - ii) High risk of bias e.g. participants assigned to treatments on the basis of date of birth, clinic id-number or surname, or no attempt to randomise participants
 - iii) Unclear risk of bias e.g. not reported, information not available
- Allocation concealment
 - i) Low risk of bias e.g. where the allocation sequence could not be foretold
 - ii) High risk of bias e.g. allocation sequence could be foretold by patients, investigators or treatment providers
 - iii) Unclear risk of bias e.g. not reported.
- Blinding of participants and personnel
 - i) Low risk of bias if participants and personnel were adequately blinded
 - ii) High risk of bias if participants were not blinded to the intervention that the participant received
 - iii) Unclear risk of bias if this was not reported or unclear
- Blinding of outcomes assessors
 - i) Low risk of bias if outcome assessors were adequately blinded
 - ii) High risk of bias if outcome assessors were not blinded to the intervention that the participant received
 - iii) Unclear risk of bias if this was not reported or is unclear
- Incomplete outcome data: we will record the proportion of participants whose outcomes were not reported at the end of the study. We will code a satisfactory level of loss to follow-up for each outcome as:
 - i) Low risk of bias e.g. if fewer than 20% of participants were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms
 - ii) High risk of bias e.g. if more than 20% of participants were lost to follow-up or reasons for loss to follow-up differed between treatment arms
 - iii) Unclear risk of bias e.g. if loss to follow-up was not reported
- Selective reporting of outcomes
 - i) Low risk of bias e.g. review reports all outcomes specified in the protocol
 - ii) High risk of bias e.g. the study is suspected that outcomes have been selectively reported
 - iii) Unclear risk of bias e.g. it is unclear whether outcomes have been selectively reported
- Other bias
 - i) Low risk of bias e.g. the review authors do not suspect any other source of bias and the trial appears to be methodologically sound
 - ii) High risk of bias e.g. the review authors suspect that the trial was prone to an additional bias
 - iii) Unclear risk of bias e.g. the review authors are uncertain whether an additional bias may have been present

CONTRIBUTIONS OF AUTHORS

Chumnan Kietpeerakool: developed and completed the review

Bandit Chumworathayi: conceived the review question, developed, co-ordinated the review.

Jadsada Thinkamrop: performed part of the editing of the review and advised on part of the review.

Butsakorn Ussahgij: searched for potential eligible studies and advised on part of the review

Pisake Lumbiganon: co-ordinated the development of the review, edited the review, and advised on the review.

All authors approved the final version of the review prior to submission.

DECLARATIONS OF INTEREST

CK: None known

BC: None known

JT: None known

BU: None known

PL: None known

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- Cochrane Thailand, Thailand.

External sources

- Thailand Research Fund (Distinguished Professor Award), Thailand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of interventions

In the review, we additionally stated the details of antibiotic regimen as “Antibiotic regimen includes the followings: administration route (for example intravenous, intramuscular, oral, vaginal); number of doses (for example, single versus multiple doses).

Types of outcome measures

In the review protocol, we stated that primary outcome was genital infections occurring within seven days of excision of the cervical transformation zone including (a) cervix: cervicitis 24 hours following the procedure as defined by one or more of the symptoms and signs; delayed bleeding; redness; pus or offensive discharge; positive gram stain; positive culture; (b) uterus or adnexa: pelvic inflammatory disease (PID) assessed by vaginal examination for all women 24 hours after the procedure, found to have clinical evidence of PID (cervical excitation, pelvic organ tenderness, or both); and (c) sepsis or other serious infection or infectious complications, either with or without fever, defined as body temperature higher than 38° Celsius on at least two occasions more than four hours apart, 24 hours after the procedure. Secondary outcome was adverse effects of antibiotics including adverse drug reactions, which were defined as any medical complications related to drug metabolisms; allergy, liver failure, renal failure, etc. according to the CTCAE version 4 (CTCAE 2010) and drug interactions.

In attempts to cover a broad range of outcome measures for infectious complications following excision of the cervical transformation zone, we revised this section in this review as follows; Primary outcomes: (1) Infectious complications (defined as any documented sites of infection identified by cultivation or clinical symptoms and signs, or both), measured as the proportion of participants who developed each of the following within eight weeks of surgery: cervicitis, endometritis, pelvic inflammatory disease, prolonged vaginal discharge, severe vaginal bleeding, lower abdominal pain, fever, and additional antibiotic treatment; (2) Antibiotic resistance.

Secondary outcomes included (1) Adverse effects-related to antibiotics: classified according to Common Terminology Criteria for Adverse Events (CTCAE 2010) as follows: gastrointestinal disorders (nausea, vomiting, anorexia, diarrhoea); immune system disorders (allergic reaction, anaphylaxis) blood and lymphatic system disorders (leucopenia, anaemia, thrombocytopenia, neutropenia); skin (stomatitis, mucositis, alopecia, allergy); nervous system disorders; genitourinary; and other side effects not categorised above; (2) unscheduled medical consultant (for any reasons); and (3) additional self-medication .

Searching other source

In the review, we added Index to theses (ProQuest Dissertations & Theses: UK & Ireland) and the WHO International Clinical Trial Registry (<http://apps.who.int/trialsearch/Default.aspx>) as additional databases to be searched. In addition, we added the lists of conferences used for searching abstracts and proceedings

Data synthesis

We additionally stated in the review that "we prepared a 'Summary of findings' table to present the results of the meta-analysis, based on the methods described in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schunemann 2011). We presented the results of the meta-analysis for the primary outcome and adverse events as outlined in the 'Types of outcome measures' section".

Assessment of reporting biases

As there was only three trials that met our inclusion criteria, we were unable to construct funnel plots to determine the possibility of publication bias as previously stated in the review protocol. In future update of this review, we will construct funnel plots corresponding to meta-analyses of the primary outcome to assess the possibility of publication bias if we identify a sufficient number of included studies (i.e. more than 10). We will also carry out sensitivity analyses to investigate the effect on the pooled results if the funnel plots are asymmetrical.

Subgroup analysis and investigation of heterogeneity

All three included trials in this review relate primarily to cervical transformation zone excision using electrical wire loop. Therefore, subgroup analyses according to the types of excisional techniques as mentioned in the review protocol was not feasible.



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Immediate versus delayed postpartum insertion of contraceptive implant for contraception (Review)

Sothornwit J, Werawatakul Y, Kaewrudee S, Lumbiganon P, Laopaiboon M

Sothornwit J, Werawatakul Y, Kaewrudee S, Lumbiganon P, Laopaiboon M.

Immediate versus delayed postpartum insertion of contraceptive implant for contraception.

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	4
BACKGROUND	6
OBJECTIVES	6
METHODS	7
RESULTS	9
Figure 1.	10
Figure 2.	12
Figure 3.	13
Figure 4.	15
Figure 5.	15
Figure 6.	16
DISCUSSION	17
AUTHORS' CONCLUSIONS	19
ACKNOWLEDGEMENTS	19
REFERENCES	19
CHARACTERISTICS OF STUDIES	21
DATA AND ANALYSES	28
Analysis 1.1. Comparison 1 Immediate versus delayed postpartum insertion of contraceptive implants, Outcome 1 Rate of initiation of contraceptive implants.	29
Analysis 1.2. Comparison 1 Immediate versus delayed postpartum insertion of contraceptive implants, Outcome 2 Continuation rate.	30
Analysis 1.3. Comparison 1 Immediate versus delayed postpartum insertion of contraceptive implants, Outcome 3 Side effect: mean days of abnormal vaginal bleeding.	31
Analysis 1.4. Comparison 1 Immediate versus delayed postpartum insertion of contraceptive implants, Outcome 4 Other side effects.	32
Analysis 1.5. Comparison 1 Immediate versus delayed postpartum insertion of contraceptive implants, Outcome 5 Participant's satisfaction.	33
Analysis 1.6. Comparison 1 Immediate versus delayed postpartum insertion of contraceptive implants, Outcome 6 Unintended pregnancy rate.	33
Analysis 1.7. Comparison 1 Immediate versus delayed postpartum insertion of contraceptive implants, Outcome 7 Breastfeeding at six months postpartum.	34
APPENDICES	34
CONTRIBUTIONS OF AUTHORS	35
DECLARATIONS OF INTEREST	35
SOURCES OF SUPPORT	35
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	35

Immediate versus delayed postpartum insertion of contraceptive implant for contraception

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ABSTRACT

Background

The spacing of pregnancies has a positive impact on maternal and newborn health. The progestin contraceptive implant, which is a long-acting, reversible method of contraception, has a well-established low failure rate that is compatible with tubal sterilization. The standard provision of contraceptive methods on the first postpartum visit may put some women at risk of unintended pregnancy, either due to loss to follow-up or having sexual intercourse prior to receiving contraception. Therefore, the immediate administration of contraception prior to discharge from the hospital that has high efficacy may improve contraceptive prevalence and prevent unintended pregnancy.

Objectives

To compare the initiation rate, effectiveness, and side effects of immediate versus delayed postpartum insertion of implant for contraception.

Search methods

We searched for eligible studies up to 28 October 2016 in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, and POPLINE. We examined review articles and contacted investigators. We also checked registers of ongoing clinical trials, citation lists of included studies, key textbooks, grey literature, and previous systematic reviews for potentially relevant studies.

Selection criteria

We sought randomised controlled trials (RCTs) that compared immediate postpartum versus delayed insertion of contraceptive implant for contraception.

Data collection and analysis

Two review authors (JS, YW) independently screened titles and abstracts of the search results, and assessed the full-text articles of potentially relevant studies for inclusion. They extracted data from the included studies, assessed risk of bias, compared results, and resolved disagreements by consulting a third review author (PL or SK). We contacted investigators for additional data, where possible. We computed the Mantel-Haenszel risk ratio (RR) with 95% confidence interval (CI) for binary outcomes and the mean difference (MD) with 95% CI for continuous variables.

Main results

Three studies that included 410 participants met the inclusion criteria of the review. We did not identify any ongoing trials. Two included studies were at low risk of selection, attrition, and reporting biases, but were at high risk of performance and detection biases due to the inability to blind participants to the intervention. One included study was at high risk of attrition bias. The overall quality of the evidence for each comparison ranged from very low to moderate; the main limitations were risk of bias and imprecision.

Initiation rate of contraceptive implants at the first postpartum check-up visit was significantly higher in the immediate insertion group than in the delayed insertion group (RR 1.41, 95% CI 1.28 to 1.55; three studies, 410 participants; *moderate quality evidence*).

There appeared to be little or no difference between the groups in the continuation rate of contraceptive implant used at six months after insertion (RR 1.02, 95% CI 0.93 to 1.11; two studies, 125 participants; *low quality evidence*) or at 12 months after insertion (RR 1.04; 95% CI 0.81 to 1.34; one study, 64 participants; *very low quality evidence*).

Women who received an immediate postpartum contraceptive implant insertion had a higher mean number of days of abnormal vaginal bleeding within six weeks postpartum (MD 5.80 days, 95% CI 3.79 to 7.81; one study, 215 participants; *low quality evidence*) and a higher rate of other side effects in the first six weeks after birth (RR 2.06, 95% CI 1.38 to 3.06; one study, 215 participants; *low quality evidence*) than those who received a delayed postpartum insertion. There appeared to be little or no difference between the groups in heavy, irregular vaginal bleeding or associated severe cramping within 12 months (RR 1.01, 95% CI 0.72 to 1.44, one study, 64 participants; *very low quality evidence*).

It was unclear whether there was any difference between the groups in scores for participant satisfaction on a 0-10 scale (MD -0.40, 95% CI -1.26 to 0.46, *low quality evidence*), or in rates of unintended pregnancy (RR 1.82, 95% CI 0.38 to 8.71, 1 RCT, 64 women, *very low quality evidence*) at 12 months, or in rate of breastfeeding rate at six months (RR 2.01, 95% CI 0.72 to 5.63, 1 RCT, 64 women, *very low quality evidence*) rate did not differ significantly between the groups.

Authors' conclusions

Evidence from this review indicates that the rate of initiation of contraceptive implant at the first postpartum check-up visit was higher with immediate postpartum insertion than with delayed insertion. There appeared to be little or no difference between the groups in the continuation rate of contraceptive implant use at 6 months. It was unclear whether there was any difference between the groups in continuation of contraceptive use at 12 months or in the unintended pregnancy rate at 12 months.

PLAIN LANGUAGE SUMMARY

Inserting a contraceptive implant soon after childbirth

Review question

Cochrane authors compared the initiation rate, effectiveness, and side effects of insertion of a contraceptive implant (implant for birth control) soon after childbirth versus delayed insertion at postpartum visit.

Background

The spacing of pregnancies has a positive impact on health of both pregnant women and newborns. The contraceptive implant is a highly effective progestin-only method of birth control. Normally, a contraceptive implant is provided at the first (usually at six weeks) postpartum visit. However, some women do not come back, or have sex before this check-up visit. The insertion of a contraceptive implant after childbirth but before hospital discharge is worthy of consideration; it is convenient in terms of time and place, and may increase the number of women that use this method.

Study characteristics

We searched for randomised studies up to 28 October 2016. We looked at whether insertion of contraceptive implant soon after childbirth or when women come back for the first postpartum check-up affected use of this contraception method. We included three studies with a total of 410 women.

Key results

Use of a contraceptive implant was higher when it was applied right after childbirth than when it was applied four to six weeks later. There appeared to be little or no difference between the groups in the continuation rate of contraceptive implant use at 6 months. It was

unclear whether there was any difference between the groups in continuation of contraceptive use at 12 months or in the unintended pregnancy rate at 12 months.

Although vaginal bleeding and other adverse effects in the first six weeks after birth including nausea, hair loss, hirsutism, headache, and acne seem to be higher in women that receive this method a few days after childbirth rather than four to six weeks later, this finding however cannot be definitely concluded as all participants knew the nature of the intervention they received (were not blinded) and the reports of these adverse effects were not objectively assessed. It was unclear whether there was any difference between the groups at 12 months in heavy, irregular vaginal bleeding or associated severe cramping, rates of unintended pregnancy, or in measures of participants' satisfaction. Nor was it clear whether there was any difference in breastfeeding rates at 6 months. The included studies were conducted in the USA, and generalisation of these findings to other population or settings should be applied with caution.

Quality of the evidence

Overall, the quality of the evidence was moderate to very low. The main limitations were imprecision and risk of bias (related to lack of blinding and to attrition). Further good quality, well-designed randomised controlled trials will provide additional information.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Immediate postpartum insertion compared with delayed insertion of contraceptive implant for contraception						
Participant or population: postpartum women who desire a contraceptive implant for contraception Settings: hospitals in United States Intervention: immediate postpartum insertion Comparison: delayed insertion						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Delayed insertion	Immediate insertion				
Rate of initiation of contraceptive implants	69 per 100	97 per 100 (88 to 100)	RR 1.41 (1.28 to 1.55)	410 (3 studies)	⊕⊕⊕○ moderate ¹	
Continuation rate at 6 months	90 per 100	92 per 100 (84 to 100)	RR 1.02 (0.93 to 1.11)	125 (2 studies)	⊕⊕○○ low ²	
Continuation rate at 12 months	78 per 100	81 per 100 (63 to 100)	RR 1.04 (0.81 to 1.34)	64 (1 study)	⊕⊕○○ very low ^{2,4}	
Side effects: Abnormal vaginal bleeding within 6 weeks post partum	Mean 22.4	Mean 5.80 higher (95% CI 3.79 higher to 7.81 higher)	MD 5.80 (3.79 to 7.81)	215 (1 study)	⊕⊕○○ low ^{1,3}	
Side effects: Other side effects within 6 weeks	23 per 100	47 per 100 (32 to 70)	RR 2.06 (1.38 to 3.06)	215 (1 study)	⊕⊕○○ low ^{1,3}	
Side effects: Heavy, irregular vaginal bleeding or associated severe cramping within 12 months	67 per 100	68 per 100 (48 to 96)	RR 1.01 (0.72 to 1.44)	64 (1 study)	⊕⊕○○ very low ^{2,4}	

Participants' satisfaction at 12 months	Mean 8.7	Mean 0.40 lower (95% CI 1.26 lower to 0.46 higher)	MD -0.40 (-1.26 to 0.46)	64 (1 study)	⊕⊕○○ low ^{1,4}
Unintended pregnancy rate at 12 months	7 per 100	13 per 100 (3 to 61)	RR 1.82 (0.38 to 8.71)	64 (1 study)	⊕⊕○○ very low ^{2,4}
Breastfeeding at six months postpartum	15 per 100	30 per 100 (11 to 84)	RR 2.01 (0.72 to 5.63)	64 (1 study)	⊕⊕○○ very low ^{2,4}

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Abbreviations: CI: confidence interval; RR: risk ratio; MD: mean difference

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

¹Downgraded one level owing to serious imprecision (small number of participants)

²Downgraded two levels owing to very serious imprecision (small number of participants, and the CI includes appreciable benefit and harm).

³Downgraded one level owing to serious risk of assessment bias.

⁴Downgraded one level owing to serious risk of attrition bias.

BACKGROUND

Description of the condition

Traditionally, the first postpartum visit is scheduled to be at six weeks after childbirth ([Speroff 2008](#)). This visit is either to assess the recovery of the mother after childbirth or to address the contraceptive needs going forward. Although the postpartum visit is an ideal time to discuss and implement family planning services, there is a notably high default rate from postpartum appointments, particularly among adolescent mothers. This results in delayed or missed counselling opportunities about an appropriate contraception method ([Moore 2015](#); [Nkwabong 2015](#)). In addition, nearly half of women have reported to have had unprotected vaginal sexual intercourse before attending a six-week postpartum visit ([Brito 2009](#); [Chaovitsaree 2012](#)). Delayed initiation of contraception after childbirth and having unprotected sexual intercourse before attending postpartum clinic can lead to an unintended pregnancy ([Wilson 2011](#)). As unintended pregnancy may have a negative impact on newborn and maternal health ([Fraser 1995](#); [Singh 2010](#); [Finer 2011](#)), designing effective contraception practices for reducing unintended pregnancy among women who are at heightened risk is of utmost importance.

Description of the intervention

Provision of contraception usually occurs six weeks postpartum. However, a study conducted in the USA indicated that only 41% of women received contraceptives within 90 days after delivery ([Thiel de Bocanegra 2013](#)). This figure is similar to the reported results from low- and middle-income countries ([Moore 2015](#); [Nkwabong 2015](#)). Therefore immediate administration of effective contraception is worth considering.

Contraceptive implants are a long-acting, reversible, progestin-only method. Currently, two types of progestin are used as active ingredients in contraceptive implants, including levonorgestrel and etonogestrel. The primary mechanism of action of the implant is to suppress ovulation by altering the hypothalamic-pituitary-ovarian axis. The other mechanisms are to thicken cervical mucous and to alter the endometrial lining ([ACOG 2011](#)).

Contraceptive implants are extremely effective and safe. This contraceptive method offers up to three to five years of reliable pregnancy prevention once inserted. The typical-use failure rate is only 0.05% ([ACOG 2011](#)). The satisfaction rate of the implant is reported to be high. Approximately 80% of users reported satisfaction with implant leading to a high continuation rate ([Peipert 2011](#)).

Based on its high efficacy and safety, contraceptive implants are suitable for nearly all women that need contraception ([ACOG 2012](#); [WHO 2015](#)). The common side effects of contraceptive

implants include amenorrhoea, irregular menstrual bleeding, spotting, sore breasts, headache, and weight gain. However, most side effects are mild, well-tolerated, and self-resolve within the first few months of use, and women should receive counselling in order to understand the side effects.

How the intervention might work

There is an increased risk of unintended pregnancy among women who have delayed initiation of contraception after childbirth or unprotected sexual intercourse before attending a postpartum clinic. Immediate postpartum provision of highly effective contraception, including intrauterine devices (IUDs) and contraceptive implant, has been proposed ([ACOG 2011](#)).

Based on a recent Cochrane systematic review, immediate postpartum insertion of IUDs appears to be safe and effective ([Lopez 2015](#)). Advantages of this practice include high motivation and convenience for both postpartum women and providers. However, the expulsion rate of IUDs inserted immediately postpartum is slightly higher than in women that have deferred insertion of IUDs ([Lopez 2015](#)).

Immediate postpartum provision of the contraceptive implant has no significant negative impact on outcomes regarding maternal health and infant weight gain ([Brito 2009](#)). The World Health Organization's (WHO's) medical eligibility criteria for contraceptive use support contraceptive implant insertion prior to hospital discharge regardless of lactating status ([Whaley 2015](#); [WHO 2015](#)). The side effects of immediate postpartum insertion of contraceptive implants also appear to be similar to that of interval insertion ([Ireland 2014](#)). Additionally, the three-year continuation rate of this method is as high as 66% when contraceptive implants are inserted immediately postpartum, which emphasizes a high level of women's satisfaction with this practice ([Wilson 2014](#)).

Why it is important to do this review

Immediate postpartum insertion of a contraceptive implant could be a promising choice of timing of contraceptive method initiation. This is quite crucial for postpartum women who are at high risk of missing the six-week postpartum visit, or of having early unprotected intercourse after childbirth, or both.

However, to our knowledge, there has been no systematic review to date that has evaluated the effectiveness and safety of immediate postpartum insertion of contraceptive implant for contraception.

OBJECTIVES

To compare the initiation rate, effectiveness, and side effects of immediate versus delayed postpartum insertion of implant for contraception.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs), irrespective of blinding, language, publication status, or sample size. We did not include controlled clinical trials (CCTs) that used non-random methods of assigning participants to treatment, such as by alternation, by birth date, or by medical record number, as they may be subject to high risk of bias.

Types of participants

Postpartum women who requested a reversible contraceptive method and were recruited before hospital discharge.

Types of interventions

Immediate postpartum insertion of contraceptive implant (after delivery to before hospital discharge) compared to delayed post-partum insertion (during postpartum visit after hospital discharge), which is often referred to as standard or interval insertion.

Types of outcome measures

Primary outcomes

- Rate of contraceptive implant initiation at the first postpartum check-up visit.

Secondary outcomes

- Continuation rate at 6, 12, and 24 months after delivery.
- Side effects, such as abnormal vaginal bleeding.
- Participant satisfaction.
- Rate of pregnancy at 6, 12, and 24 months after delivery.
- Unintended pregnancy rate at 6, 12, and 24 months after delivery.
- Rapid repeat pregnancy (defined as pregnancy onset within two years of the previous pregnancy (Baldwin 2013)).
- Breastfeeding at six months postpartum

Search methods for identification of studies

Electronic searches

We searched the following electronic databases;

- The Cochrane Central Register of Controlled Trials (CENTRAL, 2016, issue 10);
- MEDLINE (1946 to October week 4, 2016)
- Embase (1980 to October 2016),
- POPLINE (1970 to October 2016)

We have provided the search strategies in [Appendix 1](#).

Searching other resources

We checked the citation lists of included studies, key textbooks, and systematic reviews for potentially relevant references. We searched the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (<http://www.who.int/ictrp/en/>) and ClinicalTrials.gov to identify ongoing trials. We applied modified versions of the same search strategy to check the following databases for grey literature: OpenGrey, GreyNet, Scirus, Social Care Online, National Research Register, NIHR portfolio database, and Index to theses.

Data collection and analysis

Selection of studies

Before examining the identified trials for possible inclusion, we developed and piloted a data collection form, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We downloaded all titles and abstracts retrieved by electronic searching to EndNote (EndNote 2015), a reference management database, and removed duplicates. Two review authors, JS and YW, independently screened the titles and abstracts of the remaining studies. We excluded studies that clearly did not meet the inclusion criteria. We obtained full-text copies of potentially relevant studies. Two review authors, JS and YW, independently assessed the eligibility of the retrieved reports/publications. We resolved any disagreement through discussion or, if required, we consulted a third review author (PL). We identified and intended to collate multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Liberati 2009) and a 'Characteristics of excluded studies' table.

Data extraction and management

Two review authors, JS and YW, independently extracted study characteristics and outcome data from included studies using a piloted data collection form. We noted in the 'Characteristics of included studies' table if the included trials did not report outcome data in a usable way. We then contacted the trial authors for further information. We resolved disagreements by consensus or by involving a third review author (PL or SK). One review author,

ML, entered data into Review Manager 5 (RevMan 5) (RevMan 2014). We double-checked whether data is entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (PL or SK) checked all study characteristics for accuracy against the trial report.

For included studies, we extracted the following data.

- Author, year of publication, and journal citation (including language).
- Country.
- Setting.
- Inclusion and exclusion criteria.
- Study design and methodology.
- Study population.
- Study outcomes and their related summary statistics.

Assessment of risk of bias in included studies

We assessed and reported on the methodological risk of bias of included studies in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), which recommends the explicit reporting of the following individual elements for RCTs.

- Selection bias: random sequence generation and allocation concealment.
- Performance bias: blinding of participants and personnel (participants and treatment providers).
- Detection bias: blinding of outcome assessors.
- Attrition bias: incomplete outcome data.
- Reporting bias: selective reporting of outcomes.

Two review authors, JS and YW, independently applied the 'Risk of bias' tool to each included study and resolved differences by discussion or by consulting a third review author (PL or ML). We judged each item as at either 'high', 'low', or 'unclear' risk of bias, as set out in the criteria provided by Higgins 2011, and provided a quote from the study report or a statement as justification for the judgement for each item in the 'Risk of bias' table. We summarized the results in both a 'Risk of bias' graph and a 'Risk of bias' summary. When we interpreted treatment effects and meta-analyses, we took into account the risk of bias for the studies that contributed to that outcome. Where information on risk of bias was related to unpublished data or correspondence with a trial author, we noted this in the 'Risk of bias' table.

Measures of treatment effect

We used the following measures of the effect of treatment.

- For dichotomous outcomes, such as the rate of contraceptive implant initiation, we used number of events and number of participants assessed for both the intervention and comparison groups to calculate the risk ratio (RR) and 95% confidence interval (CI).
- For continuous outcomes, such as satisfaction rate, we used mean, standard deviation (SD), and the number of participants

assessed for both the intervention and comparison groups to calculate mean difference (MD) with 95% CI.

Unit of analysis issues

We intended to include studies where individual postpartum women were randomised and cluster-randomised studies where, for example, the hospital was the unit of randomisation. However, we did not find any cluster randomised studies that met the review inclusion.

Dealing with missing data

We did not impute any missing outcome data and we tried to contact the trial authors for missing data.

Assessment of heterogeneity

We assessed heterogeneity by visual inspection of the forest plots. We also assessed statistical heterogeneity in each meta-analysis using the I^2 statistic and χ^2 test. We regarded heterogeneity as substantial if the I^2 statistic value was greater than 50%, or there was a low P value (less than 0.10) in the χ^2 test for heterogeneity (Deeks 2001).

Assessment of reporting biases

As only three RCTs met the review inclusion criteria, we were unable to construct funnel plots to determine the possibility of publication bias.

Data synthesis

We undertook meta-analysis for all the outcomes where suitable data were available. We described in narrative skewed data reported as medians and interquartile ranges.

Using RevMan 5 we performed statistical analyses (RevMan 2014). We used a fixed-effect model to combine data where it is reasonable to assume that studies were estimating the same underlying treatment effect i.e. where studies were examining the same intervention, and we judged the studies' populations and methods to be sufficiently similar. If there was unexplained clinical heterogeneity sufficient to expect that the underlying treatment effects differed between studies, or if substantial statistical heterogeneity sufficient to expect that the underlying treatment effects differed between studies, or if we detected substantial statistical heterogeneity, we used a random-effects meta-analysis to produce an overall summary if we considered an average treatment effect across trials to be clinically meaningful. We used the random-effects meta-analysis, treated the pooled treatment effect as the average range of possible treatment effects, and discussed the clinical implications of treatment effects differing between studies. If the average treatment effect was not clinically meaningful, we did not intend to combine study results. If we used random-

effects analyses, we presented the results as the pooled treatment effect with 95% CIs, and the estimates of the T^2 and I^2 statistic (DerSimonian 1986). We prepared a 'Summary of findings' table to present the results of meta-analysis, based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011). For the data that we were unable to pool for meta-analysis, we conducted a narrative synthesis of the results.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses according to age of participants (teenagers versus non-teenagers) and population differences (high-income versus low- and middle-income countries). We did not perform these subgroup analyses due to the limited number of included studies.

Sensitivity analysis

We planned to perform sensitivity analyses in order to determine the impact of the following factors on effect size:

1. Repeating the analysis excluding unpublished studies (if any).
2. Repeating the analysis excluding trials rated as 'high' or 'unclear' for risk of selection bias

There were too few studies to perform these sensitivity analyses.

Overall quality of the evidence: 'Summary of findings' table

Two review authors working independently prepared a 'Summary of findings' table, with disagreements were resolved by consensus. The following outcomes were reported on the table: rate of initiation of contraceptive implants, continuation rate at 6 months, continuation rate at 12 months, side-effects: abnormal vaginal bleeding within 6 weeks postpartum, side effects other than abnormal

vaginal bleeding, participant's satisfaction, unintended pregnancy rate and breastfeeding at six months postpartum.

We used the GRADE approach (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the evidence (GRADEproGDT 2014). We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We justified all decisions to downgrade the quality of evidence, using footnotes.

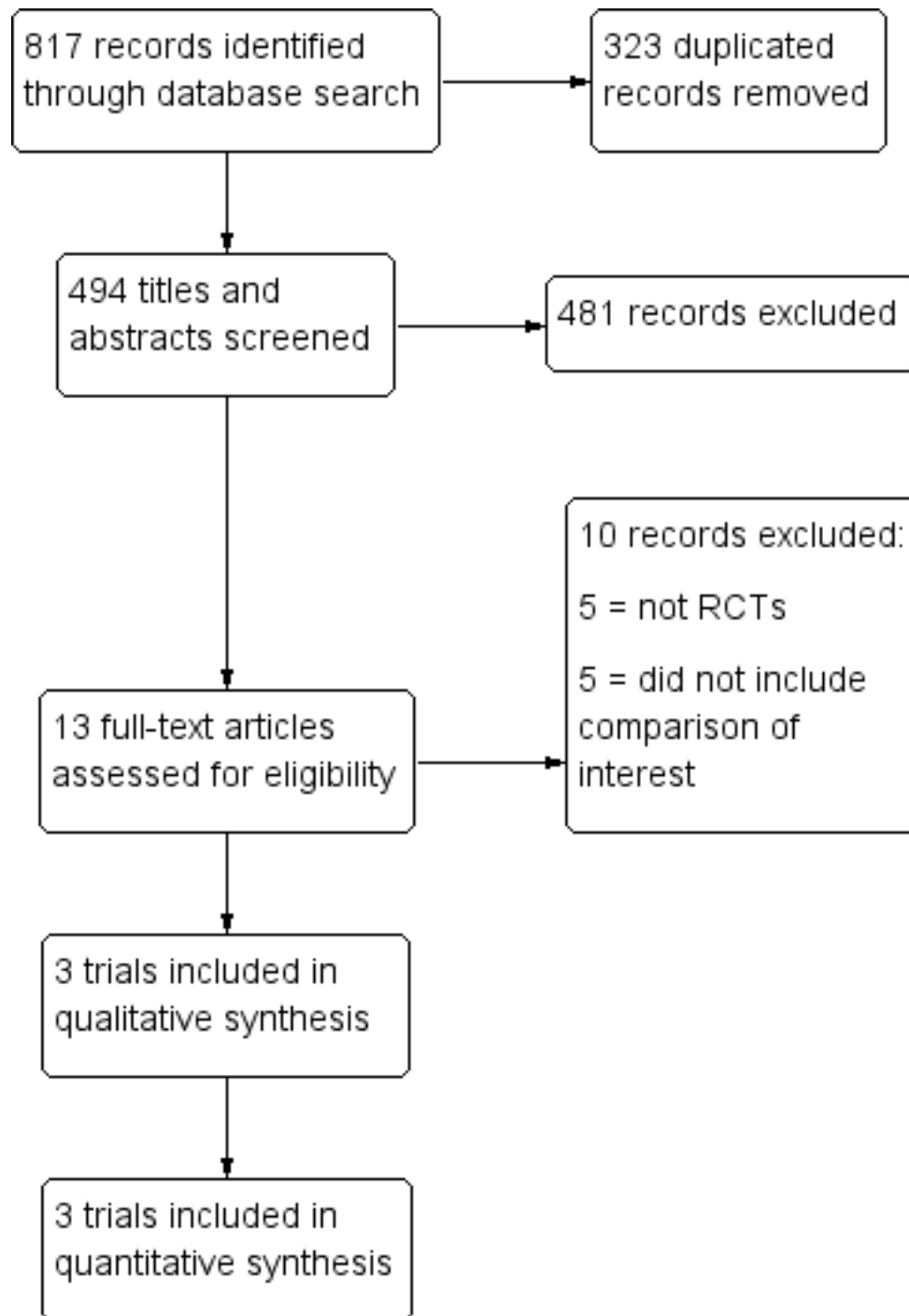
RESULTS

Description of studies

Results of the search

We identified 817 references from the combined searches. After we removed 323 duplicated references, we screened the titles and abstracts of 494 references and discarded 481 references as they obviously did not meet the review inclusion criteria. Of the 13 studies that potentially met the review inclusion criteria, we excluded 10 studies after we reviewed the full texts of these studies (see the 'Characteristics of excluded studies' table), thereby leaving three studies that met the inclusion criteria of this review (Phemister 1995; Gurtcheff 2011; Bryant 2016); see the 'Characteristics of included studies' table). We checked the reference lists of included studies, key textbooks, and systematic reviews for potentially relevant references but found no relevant studies. We did not find any ongoing trials. Figure 1 displays the PRISMA flow diagram.

Figure 1. Study flow diagram.



Included studies

We included three randomised controlled trials (RCTs) ([Phemister 1995](#); [Gurtcheff 2011](#); [Bryant 2016](#)), and presented the details of the included studies in the 'Characteristics of included studies' table.

[Phemister 1995](#) was conducted in the USA from June 1992 to February 1993. Participants were women who intended to use a contraceptive implant for postpartum contraception, had vaginal births at gestational age of 34 weeks or more, and did not have anaemia. Most women who participated in this study were black (understood to be African-American). Participants in the intervention group received immediate postpartum insertion of the levonorgestrel contraceptive implant (Norplant®, Wyeth-Ayerst, Philadelphia) between day 1 to day 3 after delivery. Participants in the control group received the same contraceptive method between four to six weeks after delivery. Reported outcomes included postpartum bleeding evaluated by the change of haemoglobin level and vaginal bleeding reported in the participant diary; postpartum contraceptive prevalence; and side effects that included nausea, hair loss, hirsutism, headache, and acne. The outcomes were evaluated during the visit scheduled at four to six weeks after delivery. [Gurtcheff 2011](#) was conducted in the USA from January to October 2009. Most participants were Hispanic. This study recruited 69 healthy peripartum women with healthy term newborns, who intended to breast feed, and desired a contraceptive implant. The contraceptive implant used was a single-rod etonogestrel (Implanon®, Schering-Plough). Participants allocated to the intervention group received immediate insertion of the etonogestrel contraceptive implant within three days after delivery. Participants assigned to the control group received the same contraceptive method four to eight weeks after delivery. The study outcomes were time to lactogenesis, lactational failure, postpartum

contraceptive prevalence, participant-reported vaginal bleeding, and breast milk creatinocrit.

[Bryant 2016](#) was conducted in USA from August 2012 to April 2015. Most participants were Hispanic or Latino. The trial included postpartum women aged 14 to 24 years who desired to use the etonogestrel contraceptive implant. Participants allocated to intervention group received the contraceptive implant prior to discharge from the hospital. Participants in control group received the same contraceptive method at four to six weeks postpartum visit. The study outcomes were contraceptive prevalence at the first postpartum check-up visit, rate of contraceptive implant use at 12 months, participants' satisfaction; abnormal bleeding patterns, breastfeeding, and unintended pregnancy rate.

Excluded studies

After assessing the full texts of 13 potentially eligible studies, we excluded 10 studies because of the following main reasons (see the 'Characteristics of excluded studies' table).

- Six studies were not RCTs or CCTs ([Shabaan 1985](#); [Taneepanichkul 2001](#); [Tocce 2012](#); [Ireland 2014](#); [Wilson 2014](#); [Garipey 2015](#)).
- Two studies compared immediate postpartum insertion of contraceptive implant as compared to no treatment ([Brito 2012](#); [Braga 2015](#)).
- Two studies compared immediate postpartum insertion of contraceptive implant as compared with depot medroxyprogesterone acetate ([Brito 2009](#); [Pentickly 2013](#)).

Risk of bias in included studies

[Figure 2](#) and [Figure 3](#) summarize the 'Risk of bias' items presented as percentages across all included studies.

Figure 2. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies.

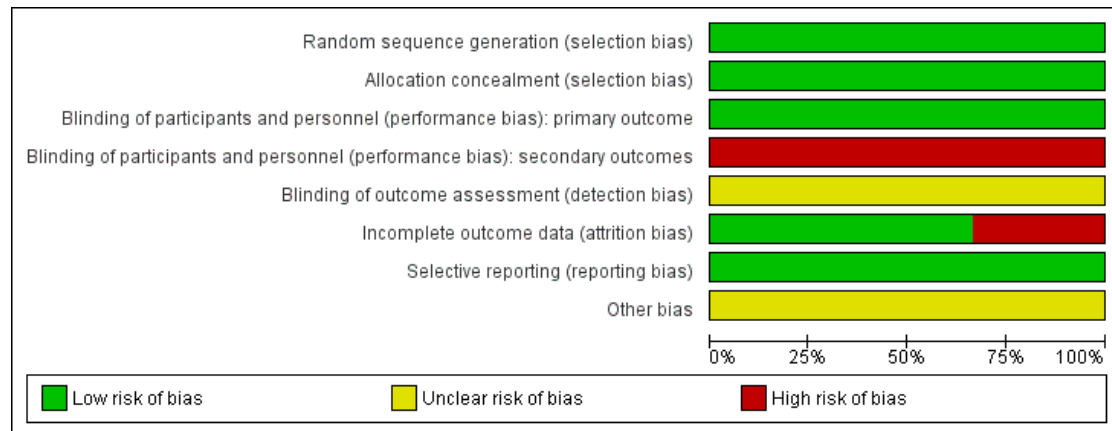


Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): primary outcome	Blinding of participants and personnel (performance bias): secondary outcomes	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bryant 2016	+	+	+	-	?	-	+	?
Gurtcheff 2011	+	+	+	-	?	+	+	?
Phemister 1995	+	+	+	-	?	+	+	?

Allocation

Random sequence generation and allocation concealment

The three included studies randomly allocated participants to the comparison groups using adequate methods for sequence generation and concealment of allocation (Phemister 1995; Gurtcheff 2011; Bryant 2016). We therefore judged all three studies as at low risk of this bias.

Blinding

Although the timing of contraceptive implant insertion could not be blinded, we judged all three included studies as at low risk of performance and detection biases for the rate of initiation of contraceptive implant, which was the primary outcome of this review, because blinding is unlikely to affect this outcome measure. However, as knowledge of group assignment may affect self-report of side effects, we therefore considered this to indicate high risk of bias for an assessment of treatment-related side effects.

Incomplete outcome data

Two included studies had rates of incomplete outcome data of less than 20% (Phemister 1995; Gurtcheff 2011). Thus, we judged both studies as at low risk of attrition bias (Figure 3). Bryant 2016 had a 33% rate of incomplete outcome data, so we determined that this study was at high risk of attrition bias.

Selective reporting

Only two study protocols of the included studies were available for assessing the outcomes of interest (Gurtcheff 2011; Bryant 2016). However, the trial investigators of all included studies reported all relevant outcomes for their objectives, so we judged this domain as at low risk of selection bias.

Other potential sources of bias

In Phemister 1995, the trial investigators excluded nine women after randomisation. The trial investigators of all included studies did not state the definitions of abnormal vaginal bleeding patterns

applied in their studies, which was the outcome of interest of this review (Phemister 1995; Gurtcheff 2011; Bryant 2016). We therefore assessed this domain as at unclear risk of bias in each of the included studies.

Effects of interventions

See: [Summary of findings for the main comparison Immediate postpartum insertion compared with delayed insertion of contraceptive implant for contraception](#)

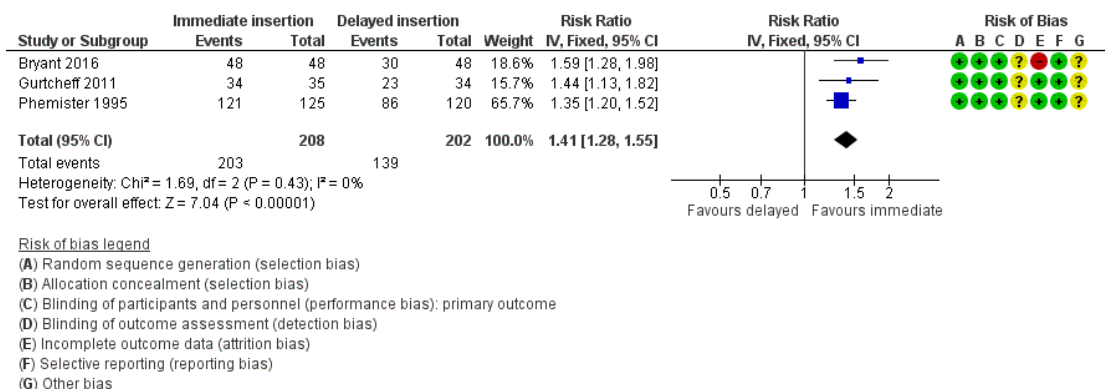
See 'Summary of findings' table 1 ([Summary of findings for the main comparison](#)).

PRIMARY OUTCOME

Rate of initiation of contraceptive implant

All included studies reported the rate of initiation of contraceptive implant at the first postpartum check-up visit (four to six weeks postpartum in Phemister 1995 and Bryant 2016 and four to eight weeks postpartum in Gurtcheff 2011). In Phemister 1995, 121 of 125 (96.8%) women assigned to the immediate postpartum insertion of contraceptive implant received contraceptive implant insertion as per the study protocol, while only 86 of 120 (71.7%) women assigned to the delayed postpartum insertion received implant insertion between four to six weeks postpartum at the time of the scheduled postpartum follow-up visit. These findings were in line with that noted in Gurtcheff 2011, which observed that the rate of initiation of contraceptive implants was remarkably high among women assigned to immediate postpartum insertion when compared to women in the delayed postpartum insertion group (97.1% versus 67.6%, respectively). In Bryant 2016, all 48 women assigned to immediate insertion group received contraceptive implant insertion compared to only 32 of 48 women (67%) allocated to delayed insertion group. There was a higher rate of contraceptive implant initiation among women assigned to immediate insertion group compared with those in the delayed insertion group (risk ratio (RR) 1.41, 95% confidence interval (CI) 1.28 to 1.55; three studies, 410 participants; *moderate quality evidence*; [Analysis 1.1](#); [Figure 4](#); [Summary of findings for the main comparison](#)).

Figure 4. Forest plot of comparison: I Immediate versus delayed postpartum insertion of contraceptive implants, outcome: I.1 Rate of initiation of contraceptive implants.



was 97.1% for women allocated to the immediate postpartum insertion, which was comparable to the rate of 95.7% reported for women in the delayed postpartum insertion group. In [Bryant 2016](#), the continuation rate among women who received an immediate insertion was similar to that in women assigned to delayed insertion group (88% versus 86%, respectively). The meta-analysis using fixed-effects model suggested little or no difference between the groups in the rate of continuation of contraceptive implant use at six months following delivery (RR 1.02, 95% CI 0.93 to 1.11; two studies, 125 participants; *low quality evidence*; [Analysis 1.2](#); [Figure 5](#); [Summary of findings for the main comparison](#)).

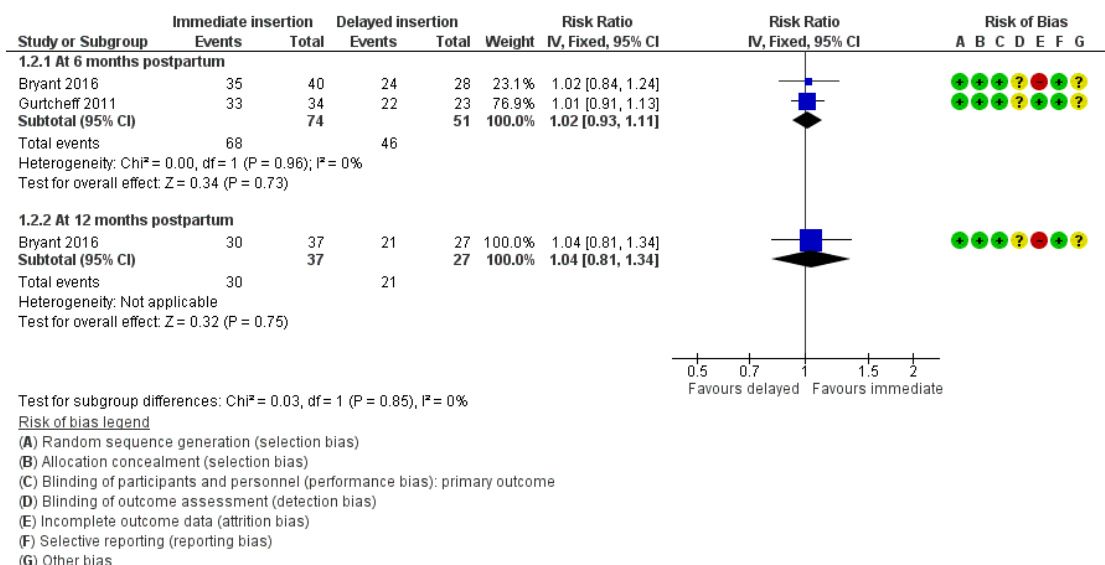
SECONDARY OUTCOMES

Continuation rate

Continuation rate at six months after delivery

[Gurtcheff 2011](#) and [Bryant 2016](#) reported the continuation rate of contraceptive implant used at six months. The six-month continuation rate of contraceptive implant use in [Gurtcheff 2011](#)

Figure 5. Forest plot of comparison: I Immediate versus delayed postpartum insertion of contraceptive implants, outcome: I.2 Continuation rate.



Continuation rate at 12 months after delivery

Only [Bryant 2016](#) reported the continuation rate of contraceptive implant use at 12 months after delivery. The 12-month continuation rate of contraceptive implant use among women receiving immediate insertion was 81.1%, and it was 77.8% in women receiving delayed insertion. It was unclear whether there was any difference between the groups (RR 1.04; 95% CI 0.81 to 1.34; one study, 64 participants; *very low quality evidence*; [Analysis 1.2](#); [Figure 5](#); [Summary of findings for the main comparison](#)).

Continuation rate at 24 months after delivery

No studies reported this outcome.

Side effects

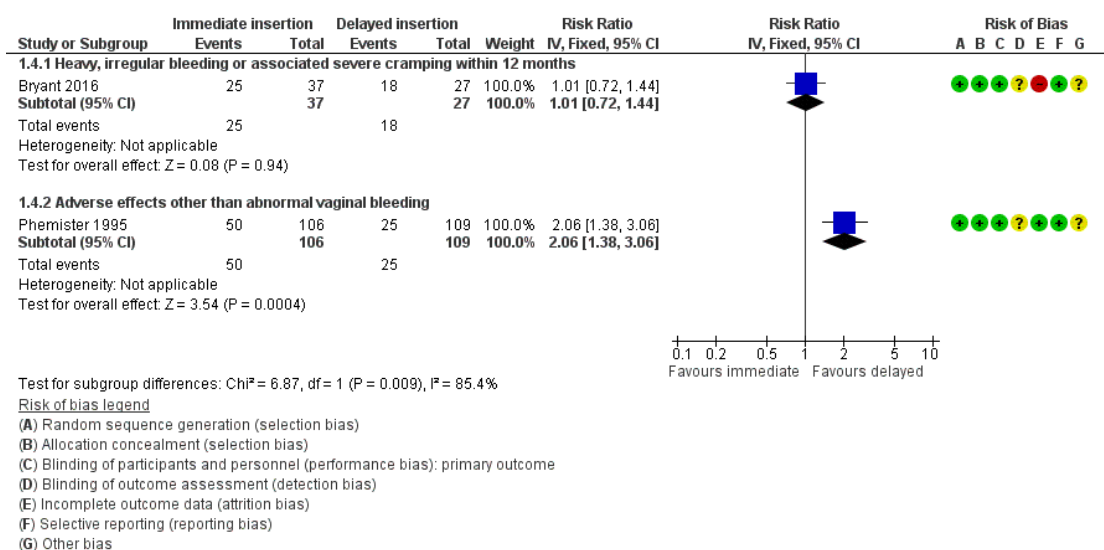
Mean days of abnormal vaginal bleeding within six weeks postpartum

One included study reported the duration of abnormal vaginal bleeding ([Phemister 1995](#)). Duration of vaginal bleeding among women in the immediate insertion group was longer than that noted among women receiving delayed insertion of contraceptive implant (mean difference (MD) 5.80 days, 95% CI 3.79 to 7.81; one study, 215 participants; *low quality evidence*; [Analysis 1.3](#); [Summary of findings for the main comparison](#)). However, this difference might not constitute a clinically important benefit as there was no distinction of follow-up haemoglobin level between these two comparison groups ([Phemister 1995](#)).

Heavy, irregular vaginal bleeding or associated severe cramping within 12 months

[Bryant 2016](#) the rate of heavy, irregular bleeding, or associated cramping evaluated at 12 months among women receiving immediate insertion compared to women receiving delayed insertion of contraceptive implant. It was unclear whether there was any difference between the groups (RR 1.01, 95% CI 0.72 to 1.44; one study, 64 participants; *very low quality evidence*; [Analysis 1.4](#); [Figure 6](#)).

Figure 6. Forest plot of comparison: I Immediate versus delayed postpartum insertion of contraceptive implants, outcome: I.4 Other side effects.



Other side effects

[Phemister 1995](#) reported that women in the immediate insertion group experienced a significantly higher rate of adverse effects other than vaginal bleeding including nausea, hair loss, hirsutism, headache, and acne than reported among women receiving delayed insertion (RR 2.06; 95% CI 1.38 to 3.06; one study, 215 participants; *low quality evidence*; [Analysis 1.4](#); [Figure 6](#); [Summary of findings for the main comparison](#)).

Participant satisfaction

In [Bryant 2016](#), the trial investigators asked their participants to rate the satisfaction score from zero to 10 during the one year follow-up. There was little or no difference between the groups in participant satisfaction score (MD -0.40, 95% CI -1.26 to 0.46; one study, 64 participants; *low quality evidence*; [Analysis 4.1](#); [Summary of findings for the main comparison](#)).

Unintended pregnancy rates

Unintended pregnancy rates at 12 months after delivery

[Bryant 2016](#) reported that the rates of unintended pregnancy occurring within one year after delivery were 13.5% and 7.0% among participants allocated to immediate insertion and those who were assigned to delayed insertion group, respectively. It was unclear whether there was any difference between the groups (RR 1.82, 95% CI 0.38 to 8.71; one study, 64 participants; *low quality evidence*; [Analysis 1.6](#); [Summary of findings for the main comparison](#)).

Unintended pregnancy rates at 24 months after delivery.

No studies reported this outcome.

Rapid repeat pregnancy (defined as pregnancy onset within two years of the previous pregnancy)

No studies reported this outcome.

Breastfeeding at six months postpartum

[Gurtcheff 2011](#) and [Bryant 2016](#) reported breastfeeding rate at six months. [Gurtcheff 2011](#) presented Kaplan-Meier curves to evaluate the impact of immediate postpartum insertion of contraceptive implant on exclusive or any breastfeeding compared to that of the delayed postpartum insertion. The rates between the two groups were not significantly different at any time periods. However, numerical data regarding this outcome were insufficient to determine the relative effect at each time point. Attempts to obtain

additional data from the investigators were unsuccessful since the trial authors did not reply our requests.

[Bryant 2016](#) reported rates of breastfeeding at six months after delivery among women receiving immediate contraceptive implant insertion compared to women allocated to delayed insertion, which were 30.0% versus 15.0%, respectively. It was unclear whether there was any difference between the groups (RR 2.01, 95% CI 0.72 to 5.63; one study, 64 participants; *low quality evidence*; [Analysis 1.7](#); [Summary of findings for the main comparison](#)).

DISCUSSION

Summary of main results

Only three randomised controlled trials (RCTs) met the inclusion criteria of this review. We considered the overall review evidence to be at low risk of bias. Evidence from this review demonstrates that immediate postpartum contraceptive implant insertion significantly increases the rate of postpartum contraceptive implant initiation at the first postpartum check-up visit. The continuation rate of contraceptive implant use at six months between the two groups was comparable. The mean duration of vaginal bleeding among women receiving immediate insertion of contraceptive implant was longer than that noted among women receiving delayed insertion; however, this difference might not constitute a clinically important benefit as there was no distinction of follow-up haemoglobin level between these two comparison groups. Additionally, rates of abnormal vaginal bleeding between the two comparison groups were comparable regardless of the severity of bleeding. According to the inability to blind the intervention assigned, the difference in the rate of self-reported side effects between the immediate and delayed postpartum insertion of contraceptive implant remains inconclusive. Based on the limited data available from a small single study, there were no significant differences between the two groups in terms of participant satisfaction, unintended pregnancy rate at 12 months, and rate of breastfeeding at six months postpartum.

Overall completeness and applicability of evidence

This review included three RCTs that evaluated immediate versus delayed postpartum insertion of contraceptive implant for contraception in 410 participants in the USA. The study participants were black and Hispanic white young-adult women. Additionally, the study settings were large hospitals in the USA. None of the included studies were conducted in low- or middle-income countries, which often have low postpartum contraceptive prevalence

(UN 2013). Thus generalization of these findings to other population or settings should be applied with caution.

All included studies reported the initiation rate of contraceptive implant at the first postpartum check-up visit, which was the primary objective of this review. However, only two included studies reported the continuation rate at six months after delivery and adverse effects. Gurtcheff 2011 and Bryant 2016 reported data regarding the impact of the insertion type of contraceptive implant on breastfeeding at six months postpartum. However, we could not determine its relative effect from the only included study that reported this outcome because it lacked data regarding the actual number of participants in each comparison group (Gurtcheff 2011). Data regarding long-term continuation rate, rate of unintended pregnancy or repeat pregnancy, and participant satisfaction were limited as a single included study reported these data.

Quality of the evidence

Although there was an inability to blind the type of intervention received, it was unlikely to affect the rate of initiation of contraceptive implant and continuation rate. However, knowledge of the intervention assigned may affect self-reporting of treatment-related side effects, thus indicating a high risk of performance and assessment bias for this outcome measures. This compromises the internal validity of an included study when determining the subjective outcomes, such as side effects and participant satisfaction, since an assessment of these events was based on the outcomes retrieved from participants' self-reported data. The higher risk of side effects among women who received an immediate postpartum contraceptive implant insertion versus those who received a delayed insertion should be cautiously viewed; it is unknown whether this is because of knowledge of which intervention had been administered, or the type of contraceptive implant insertion itself, affects outcomes. We extracted data regarding the rates of continuation and unintended pregnancy, participant satisfaction, and rate of breastfeeding at six months from a small single study that had a high default rate.

We determined the quality of evidence using the GRADE approach for each outcome (see [Summary of findings for the main comparison](#)). We downgraded the quality of the evidence to moderate quality for rate of initiation of contraceptive implants. We downgraded the evidence to low or very low quality for the continuation rate of contraceptive implant, duration of abnormal vaginal bleeding, adverse effects other than vaginal bleeding, participant satisfaction, and rates of unintended pregnancy and breastfeeding at six months (see [Summary of findings for the main comparison](#)). Thus the quality of the evidence ranged from moderate to very low. The main limitations were imprecision and risk of bias (related to lack of blinding and to attrition).

Potential biases in the review process

With assistance from the Information Specialist, Cochrane Fertility Regulation Group, we made every attempt to include all potential studies including a thorough search of the standard databases, grey literature, conference proceedings, and ongoing trials. However, since only three studies met the inclusion criteria, we cannot exclude the possibility of publication bias.

None of the review authors have any links to drug companies or a financial interest in the prescription of the drugs under assessment, nor were they involved in the conduct of the included studies. Thus, there were no issues related to bias secondary to conflicts of interests in this review.

Agreements and disagreements with other studies or reviews

To date there are no systematic reviews that have compared immediate versus delayed postpartum contraceptive implant insertion. A Cochrane review that assessed the effectiveness of immediate postplacental (within 10 minutes of placenta delivery) insertion of intrauterine device (IUD) for contraception compared to early postpartum insertion (10 minutes to 48 hours) and standard insertion (during the postpartum visit) demonstrated that there was no significant difference in the rates of IUD use among women who received an immediate insertion compared to those who received an early postpartum insertion (odds ratio (OR) 0.46, 95% confidence interval (CI) 0.04 to 5.75) (Lopez 2015). However, IUD use at six months was more likely with immediate insertion of IUD than with standard insertion (OR 2.04, 95% CI 1.01 to 4.09) (Lopez 2015). In this review, the meta-analysis of both included studies revealed the significant higher rate of postpartum contraceptive implant initiation among women assigned to receive immediate insertion compared with women receiving delayed insertion (risk ratio (RR) 1.41, 95% CI 1.28 to 1.55; three studies, 410 participants). These findings therefore indicate that immediate postpartum provision of long-acting reversible contraceptive method can increase the uptake rate of postpartum contraception. Regarding pregnancy rate, Lopez 2015 reported no difference between immediate postplacental and standard insertion, which is consistent with the results of this review.

The inability to blind the intervention assigned in the included studies in this review precludes a reliable assessment of the difference in the rate of self-reported side effects between the immediate and delayed postpartum insertion of contraceptive implant. A two-year observational study conducted in the USA with 414 women showed no difference in removal rate secondary to abnormal vaginal bleeding among women who received immediate and delayed postpartum insertion of contraceptive implant (19.3% versus 18.4%, respectively) (Ireland 2014). In the prospective cohort from Thailand that evaluated the safety of immediate postpartum insertion of contraceptive implant among 88 asymptomatic HIV type 1-positive women, 62.5% of participants reported to have irregular bleeding at six months, which appeared

to be comparable to women who received a standard insertion (Taneepanichkul 2001). In this Cochrane review, although duration of vaginal bleeding among women in the immediate insertion was statistically significant longer than that noted among women who received delayed insertion of contraceptive implant (mean difference (MD) 5.80 days; 95% CI 3.79 to 7.81; one study, 215 participants), this difference might not reach a clinically important level since as there was no distinction of follow-up haemoglobin level between these two comparison groups.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence from this review indicates that the rate of contraceptive implant initiation rate was higher for women randomised to receive implants during the delivery hospitalizations compared with those randomised to receive implants at four to six weeks postpartum. This practice is a very appealing choice in areas with high default rate from postpartum follow-up appointment. Due to a high risk of performance bias and unclear risk of detection bias, the different profiles of the self-reported side effects between the immediate and delayed postpartum insertion of contraceptive implant remain inconclusive. The unintended pregnancy rate must be interpreted with caution due to the high risk of attrition bias.

Implications for research

The ultimate goal for provision of contraceptive methods is to prevent undesired pregnancy. However, questions remain about whether immediate postpartum insertion of contraceptive implants is more effective than insertion at four to six weeks postpartum in preventing unintended pregnancy and pregnancy-related morbidity and mortality. The available evidence obtained from three included studies in this review only indicates that this intervention could improve the rate of contraceptive implant initiation at the first postpartum follow visit. Further large-scale RCTs with long follow-up periods for determining the rates of long-term contraceptive implant use, unintended pregnancy, and rapid pregnancy after immediate postpartum insertion of contraceptive implant are required. In addition, the uncertainty about whether immediate postpartum contraceptive implant insertion increases the risk of adverse effects than with standard insertion also warrants further study.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bryant 2016

Methods	A randomised controlled trial (RCT) conducted in large hospital in North Carolina, USA Study duration: August 2012 to April 2014 Sample size: 96 participants were recruited to detect 30% difference in contraceptive implant use at 1 year postpartum among peripartum women assigned to receive immediate postpartum insertion (prior to hospital discharge) and delayed postpartum insertion (4 to 6 weeks) of etonogestrel contraceptive implant with a study power of 80% and alpha of 0.05
Participants	Adolescents and young women aged 14 to 24 years, gave birth to a healthy infant, spoke English or Spanish, and desired to use the contraceptive implant. Exclusion criteria included one or more of the following. • Current or past history of thrombosis or thromboembolic disorders. • Hepatic tumours. • Active liver disease. • Undiagnosed abnormal genital bleeding. • Known, suspected or history of carcinoma of the breast. • Hypersensitivity to the implant. • Use of hepatic enzyme inducers. • Maternal hospital intensive care unit (ICU) admission after delivery. • Postpartum haemorrhage requiring blood transfusion. • Hospital stay > 7 days postpartum. • Coagulopathy. • Hemolysis, elevated liver enzymes, and low platelet levels (HELLP) syndrome. Most study participants were Hispanic/Latino (40% of women assigned to both immediate and delayed postpartum insertion groups)
Interventions	Intervention arm: participants received etonogestrel contraceptive implant within 48 hours of delivery. Control arm: participants received the same contraceptive method but had been administered at 4 to 6 weeks after delivery
Outcomes	Primary outcome: contraceptive implant use at 12 months postpartum. Other outcome measures: satisfaction, bleeding patterns, breastfeeding
Notes	

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned using computer-generated random numbers in blocks of 4 and 6

Bryant 2016 (Continued)

Allocation concealment (selection bias)	Low risk	The assignments were enclosed in sequentially numbered, opaque, sealed envelopes
Blinding of participants and personnel (performance bias) primary outcome	Low risk	Although blinding of the participants was not possible, initiation rate was unlikely to be affected by the performance bias
Blinding of participants and personnel (performance bias) secondary outcomes	High risk	Blinding of the participants was not possible which may affect the self-reported side-effects
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information available.
Incomplete outcome data (attrition bias) All outcomes	High risk	There was a high rate of loss to follow-up in both groups (23% (11/48) and 44% (21/48) in immediate insertion and delayed insertion groups respectively
Selective reporting (reporting bias)	Low risk	The trial authors reported all potentially relevant outcomes
Other bias	Unclear risk	Many outcomes in this study were not analysed following an intention-to-treat basis

Gurtcheff 2011

Methods	A RCT with non-inferiority design conducted in a university hospital in Utah, USA Study duration: January to October 2009 Sample size: a total sample size of 34 participants was required in each group when the immediate postpartum insertion of the etonogestrel implant compared to delayed postpartum insertion was expected to delay time to lactogenesis stage II with a non-inferiority margin for the mean difference of 8 hours at the study power of 80% and alpha of 0.05
Participants	Healthy peripartum women with healthy, term newborns who desired the etonogestrel implant for contraception Exclusion criteria were onset of lactogenesis before randomisation, haemorrhage requiring transfusion, severe pregnancy-induced hypertension, prolonged hospitalisation, coagulopathy, liver disease, undiagnosed genital bleeding, or other relative contraindication to etonogestrel implant insertion (known or suspected pregnancy; known, suspected, or history of breast cancer; or hypersensitivity to any of the components in the etonogestrel implant). Women taking inducers of hepatic enzymes were also excluded, including barbiturates, griseofulvin, rifampin, phenylbutazone, phenytoin, carbamazepine, felbamate, oxcarbazepine, topiramate, modafinil, protease inhibitors, and herbal products Most study participants were Hispanic white (73% and 60% of women assigned to

	immediate and delayed postpartum insertion groups, respectively)
Interventions	Intervention arm: participants received etonogestrel contraceptive implant within 1 to 3 days after delivery. Control arm: participants received delayed insertion of etonogestrel contraceptive implant at 4 to 8 weeks postpartum visit
Outcomes	Primary outcome: time to lactogenesis stage II documented by maternal perception, lactational failure Other outcome measures: lactational failure, postpartum contraceptive prevalence, participant-reported vaginal bleeding, and mean creatatocrit value of breast milk at first postpartum visit
Notes	

Risk of bias**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned using computer-generated random numbers in blocks of varying sizes of 2, 4, and 6
Allocation concealment (selection bias)	Low risk	Allocation concealment was ensured because the assignments were enclosed in sequentially numbered, opaque, sealed envelopes
Blinding of participants and personnel (performance bias) primary outcome	Low risk	Although blinding of the participants was not possible, initiation rate was unlikely to be affected by the performance bias
Blinding of participants and personnel (performance bias) secondary outcomes	High risk	Blinding of the participants was not possible which may affect the self-reported side effects
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information was available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was a low rate of loss to follow-up in both groups; (17% (6/35) and 17% (6/34) in the immediate insertion and delayed insertion groups respectively
Selective reporting (reporting bias)	Low risk	The trial authors reported all potentially relevant outcomes

Other bias	Unclear risk	The trial authors did not provide the definitions of abnormal vaginal bleeding patterns applied in this study, which was an outcome of interest in this review

Phemister 1995

Methods	A RCT conducted in a large hospital in North Carolina, USA Study duration: June 1992 to February 1993 Sample size: 250 participants were recruited to detect 10% difference of prevalence of abnormal vaginal bleeding occurring among peripartum women assigned to receive immediate postpartum insertion (1 to 3 days) and delayed postpartum insertion (4 to 6 weeks) of levonorgestrel contraceptive implant with a study power of 80% and alpha of 0.05	
Participants	Peripartum women were offered inclusion in this trial if they intended to use contraceptive implant for contraception, had vaginal births, had predelivery gestational age of 34 weeks or more, had a spontaneous delivery of a grossly intact placenta, had a predelivery haemoglobin value of 8.0 g/dL or higher, and had no contraindications to Norplant insertion as listed by the manufacturer including acute liver disease, acute thromboembolic disorder, abnormal genital bleeding, pregnancy, breast cancer, or an allergy to silicone or levonorgestrel Exclusion criteria included women who intended to breastfeed, experienced postpartum haemorrhage which defined as total estimated blood loss > 500 mL or infection, currently received heparin or warfarin sodium, massively obese (postpartum weight > 250 pounds), or had a history of hypertension, seizures, or bleeding disorders 250 non-breastfeeding postpartum women who met the study inclusion were enrolled. Most women who participated in this study were black (75.2% and 72.5% of women in the immediate and delayed postpartum insertion groups, respectively)	
Interventions	Intervention arm: participants received levonorgestrel contraceptive implant within 48 hours of delivery. Control arm: participants received the same contraceptive method but had been administered at 4 to 6 weeks after delivery	
Outcomes	Primary outcome of interest was postpartum bleeding evaluated by the change of haemoglobin level and participants' self-reported of vaginal bleeding patterns Secondary outcomes included blood pressure and weight changes and participants' self-report on other side effects including nausea, hair loss, hirsutism, headaches and acne All outcomes were evaluated during the visit scheduled at 4 to 6 weeks after delivery	
Notes	The trial investigators excluded 9 women after randomisation. The included study did not state about the definitions of abnormal vaginal bleeding patterns which were the primary safety concerns of this study	

*Risk of bias**Risk of bias*

Bias	Authors' judgement	Support for judgement

Phemister 1995 (Continued)

Random sequence generation (selection bias)	Low risk	The allocation sequence was computer generated and sequences was numbered sequentially
Allocation concealment (selection bias)	Low risk	Allocation concealment was ascertained by enclosing assignments in opaque, sealed envelopes
Blinding of participants and personnel (performance bias) primary outcome	Low risk	Although blinding of the participants was not possible, initiation rate was unlikely to be affect by the performance bias
Blinding of participants and personnel (performance bias) secondary outcomes	High risk	Blinding of the participants was not possible which may affect the self-reported side effects
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information was available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up rates were 12% and 9% of participants assigned to immediate and delayed insertion groups, respectively
Selective reporting (reporting bias)	Low risk	The trial authors reported all potentially relevant outcomes
Other bias	Unclear risk	The trial investigators excluded 9 women after randomisation. In addition, no well-defined terminology of abnormal vaginal bleeding was applied in this trial

Abbreviations: RCT: randomised controlled trial.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Braga 2015	Did not compare immediate versus delayed contraceptive implant insertion
Brito 2009	Did not compare immediate versus delayed contraceptive implant insertion
Brito 2012	Did not compare immediate versus delayed contraceptive implant insertion

(Continued)

Gariepy 2015	Not a RCT.
Ireland 2014	Not a RCT.
Pentickly 2013	Did not compare immediate versus delayed contraceptive implant insertion
Shabaan 1985	Did not compare immediate versus delayed contraceptive implant insertion
Taneepanichkul 2001	Not a RCT.
Tocce 2012	Not a RCT.
Wilson 2014	Not a RCT.

Abbreviations: RCT: randomised controlled trial.

DATA AND ANALYSES

Comparison 1. Immediate versus delayed postpartum insertion of contraceptive implants

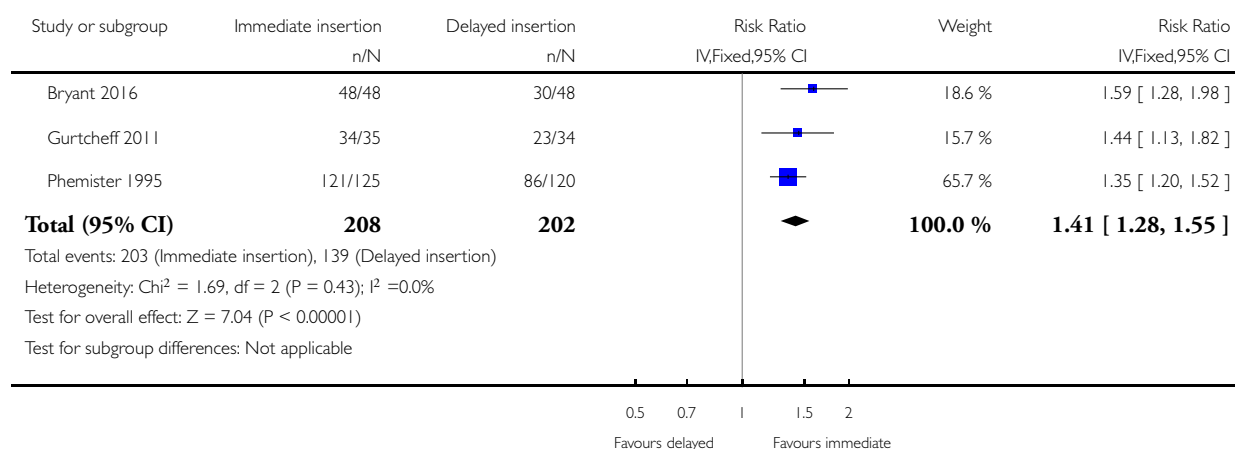
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rate of initiation of contraceptive implants	3	410	Risk Ratio (IV, Fixed, 95% CI)	1.41 [1.28, 1.55]
2 Continuation rate	2		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
2.1 At 6 months postpartum	2	125	Risk Ratio (IV, Fixed, 95% CI)	1.02 [0.93, 1.11]
2.2 At 12 months postpartum	1	64	Risk Ratio (IV, Fixed, 95% CI)	1.04 [0.81, 1.34]
3 Side effect: mean days of abnormal vaginal bleeding	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Mean days of abnormal vaginal bleeding within 6 weeks postpartum	1	215	Mean Difference (IV, Fixed, 95% CI)	5.80 [3.79, 7.81]
4 Other side effects	2		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
4.1 Heavy, irregular bleeding or associated severe cramping within 12 months	1	64	Risk Ratio (IV, Fixed, 95% CI)	1.01 [0.72, 1.44]
4.2 Adverse effects other than abnormal vaginal bleeding	1	215	Risk Ratio (IV, Fixed, 95% CI)	2.06 [1.38, 3.06]
5 Participant's satisfaction	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 At 12 months post partum	1	64	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-1.26, 0.46]
6 Unintended pregnancy rate	1		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
6.1 At 12 months after delivery	1	64	Risk Ratio (IV, Fixed, 95% CI)	1.82 [0.38, 8.71]
7 Breastfeeding at six months postpartum	1	64	Risk Ratio (IV, Fixed, 95% CI)	2.01 [0.72, 5.63]

Analysis 1.1. Comparison 1 Immediate versus delayed postpartum insertion of contraceptive implants, Outcome 1 Rate of initiation of contraceptive implants.

Review: Immediate versus delayed postpartum insertion of contraceptive implant for contraception

Comparison: 1 Immediate versus delayed postpartum insertion of contraceptive implants

Outcome: 1 Rate of initiation of contraceptive implants

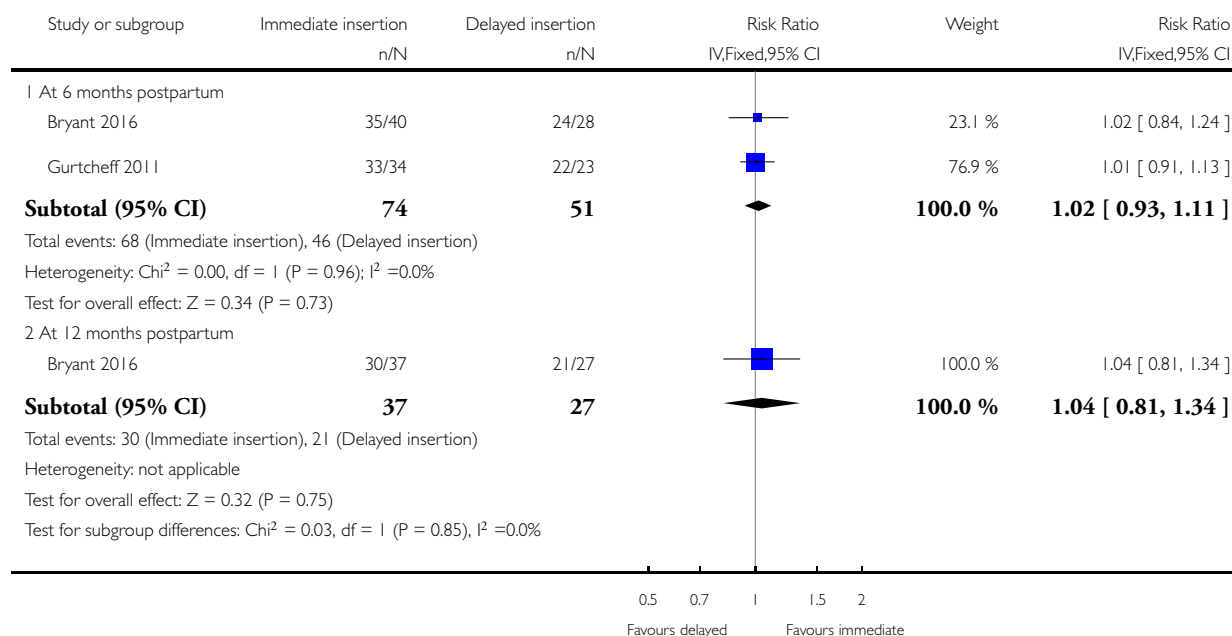


Analysis 1.2. Comparison 1 Immediate versus delayed postpartum insertion of contraceptive implants, Outcome 2 Continuation rate.

Review: Immediate versus delayed postpartum insertion of contraceptive implant for contraception

Comparison: 1 Immediate versus delayed postpartum insertion of contraceptive implants

Outcome: 2 Continuation rate

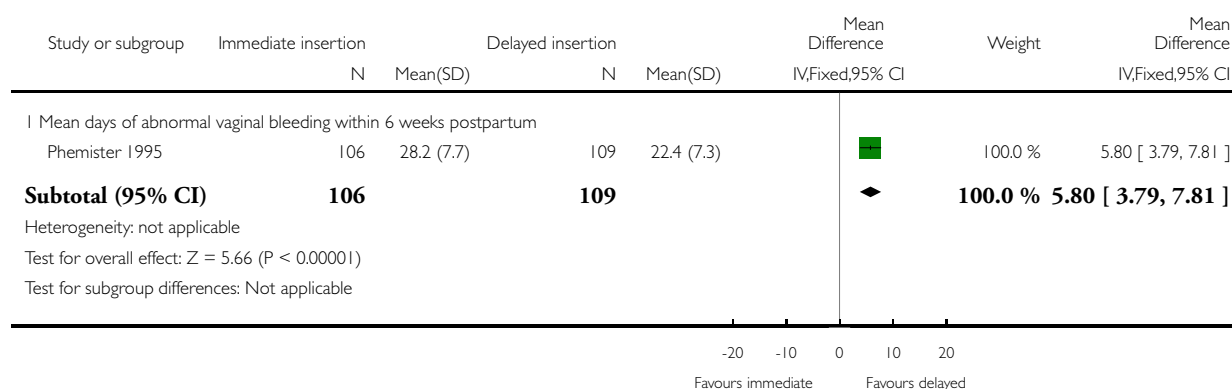


Analysis 1.3. Comparison 1 Immediate versus delayed postpartum insertion of contraceptive implants, Outcome 3 Side effect: mean days of abnormal vaginal bleeding.

Review: Immediate versus delayed postpartum insertion of contraceptive implant for contraception

Comparison: 1 Immediate versus delayed postpartum insertion of contraceptive implants

Outcome: 3 Side effect: mean days of abnormal vaginal bleeding

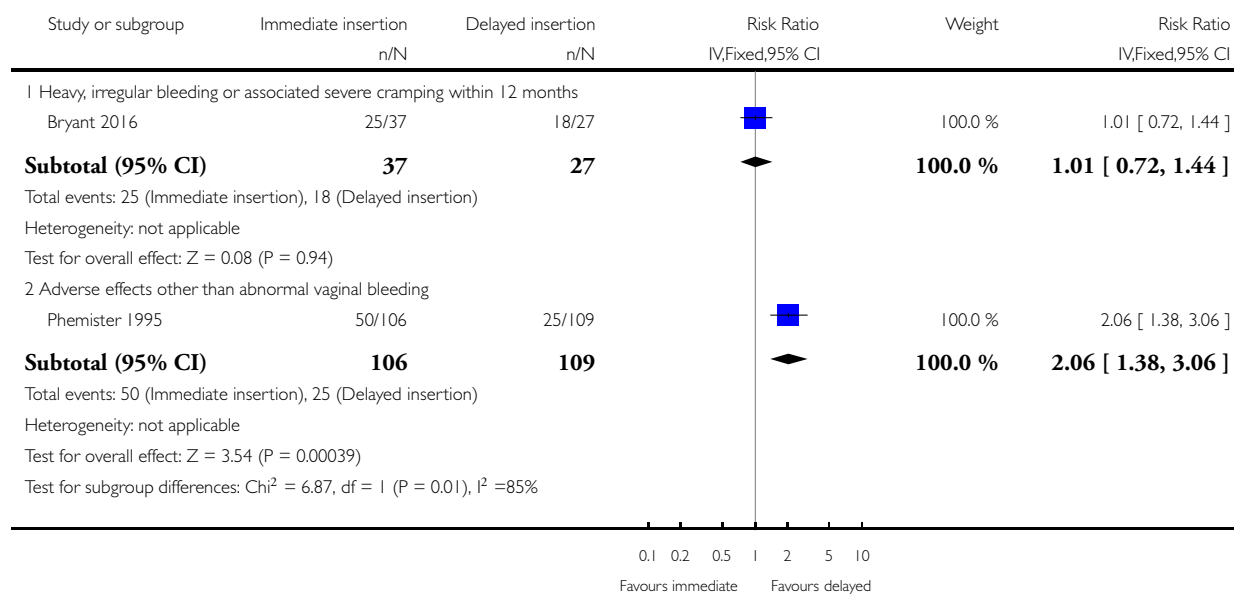


Analysis 1.4. Comparison 1 Immediate versus delayed postpartum insertion of contraceptive implants, Outcome 4 Other side effects.

Review: Immediate versus delayed postpartum insertion of contraceptive implant for contraception

Comparison: 1 Immediate versus delayed postpartum insertion of contraceptive implants

Outcome: 4 Other side effects

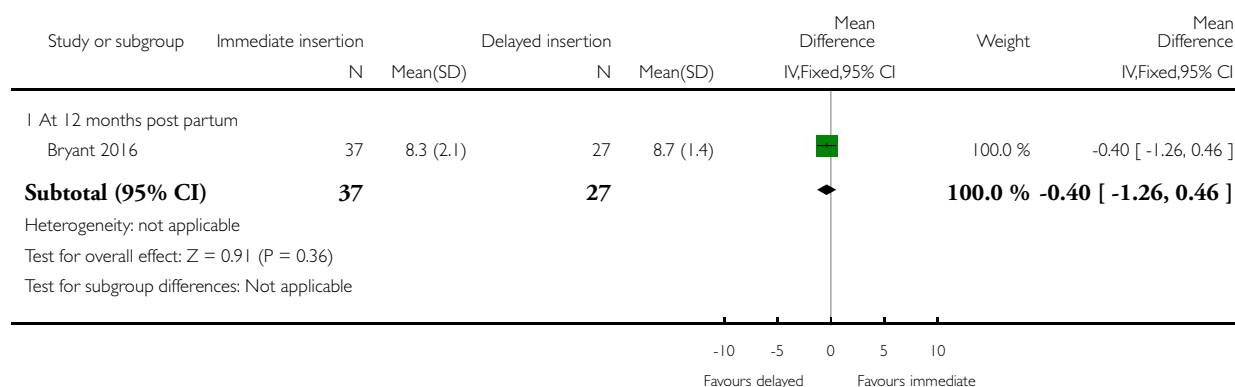


Analysis 1.5. Comparison 1 Immediate versus delayed postpartum insertion of contraceptive implants, Outcome 5 Participant's satisfaction.

Review: Immediate versus delayed postpartum insertion of contraceptive implant for contraception

Comparison: 1 Immediate versus delayed postpartum insertion of contraceptive implants

Outcome: 5 Participant's satisfaction

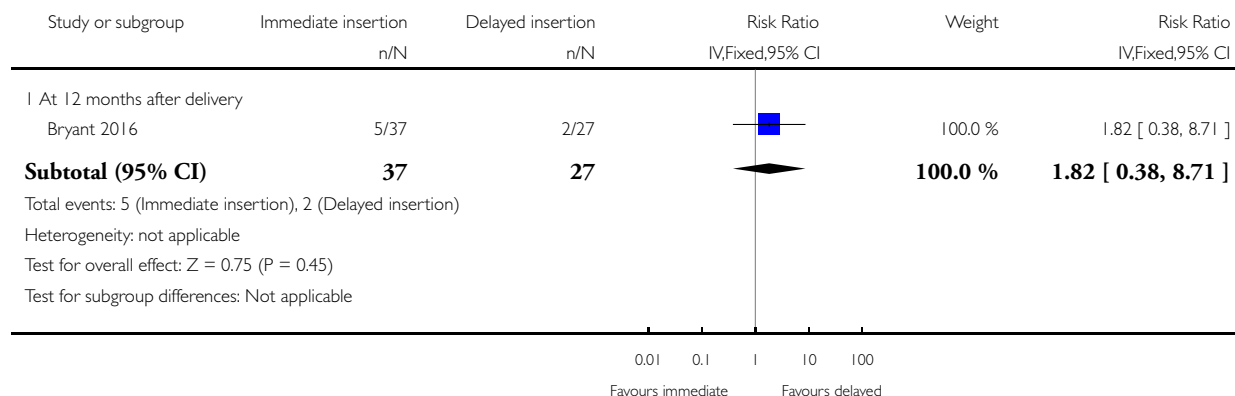


Analysis 1.6. Comparison 1 Immediate versus delayed postpartum insertion of contraceptive implants, Outcome 6 Unintended pregnancy rate.

Review: Immediate versus delayed postpartum insertion of contraceptive implant for contraception

Comparison: 1 Immediate versus delayed postpartum insertion of contraceptive implants

Outcome: 6 Unintended pregnancy rate

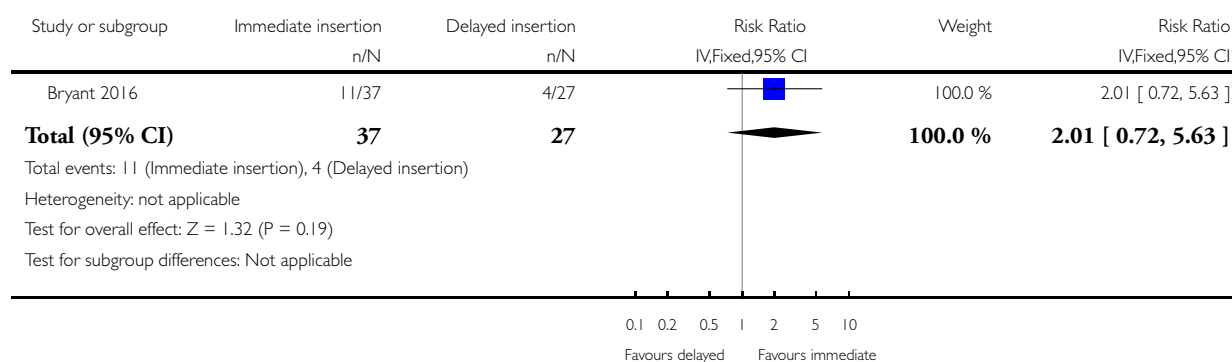


Analysis 1.7. Comparison 1 Immediate versus delayed postpartum insertion of contraceptive implants, Outcome 7 Breastfeeding at six months postpartum.

Review: Immediate versus delayed postpartum insertion of contraceptive implant for contraception

Comparison: 1 Immediate versus delayed postpartum insertion of contraceptive implants

Outcome: 7 Breastfeeding at six months postpartum



APPENDICES

Appendix 1. Search strategy

CENTRAL

(postpartum OR post-partum) AND (implant* OR (contracept* AND levonorgestrel) OR norplant OR norplants OR (keto AND desogestrel) OR etonorgestrel OR implanon OR ((subdermal OR subcutaneous) AND implant*) OR (subcutaneous AND implant) OR jadelle)

MEDLINE

(postpartum OR puerperium OR postcesarean OR delivery OR cesarean section) AND ((contracept* AND implant*) OR levonorgestrel OR norplant* OR (keto AND desogestrel) OR etonorgestrel OR implanon OR (subdermal AND implant) OR (subcutaneous AND implant) OR jadelle) AND insert*

Embase

(postpartum OR puerperium OR postcesarean OR delivery OR cesarean section) AND ((contracept* AND implant*) OR (contraceptive devices, female AND implant) OR (contracept* AND (levonorgestrel OR norplant* OR (keto AND desogestrel) OR etonorgestrel OR implanon OR (subdermal AND implant) OR (subcutaneous AND implant) OR jadelle))) AND (insert OR inserting OR inserted OR insertion)

POPLINE

("contraceptive implants" OR levonorgestrel OR norplant OR norplants OR "keto desogestrel" OR etonorgestrel OR implanon OR jadelle OR "subdermal implant" OR "subdermal implants")AND insertion AND (postpartum OR puerperium OR postcesarean OR "post cesarean")

CONTRIBUTIONS OF AUTHORS

Jen Sothornwit initiated the review topic. Jen Sothornwit, Yuthapong Werawatakul, Srinaree Kaewrudee, Malinee Laopaiboon and Pisake Lumbiganon drafted the review. All authors reviewed and approved the final version of the review.

DECLARATIONS OF INTEREST

Jen Sothornwit: none known

Yuthapong Werawatakul: none known

Srinaree Kaewrudee: none known

Pisake Lumbiganon: none known

Malinee Laopaiboon: none known

SOURCES OF SUPPORT

Internal sources

- Department of Obstetrics and Gynecology, Faculty of Medicine, Khon Kaen University, Thailand.
- Department of Epidemiology and Biostatistics, Faculty of Public Health, Khon Kaen University, Thailand.

External sources

- Thailand Research Fund (Distinguished Professor Awards), Thailand.
- Cochrane Thailand, Thailand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Primary review outcome

In our protocol the primary outcome was 'Postpartum contraceptive prevalence at the first postpartum check-up visit'. This has been re-worded as 'Rate of contraceptive implant initiation at the first postpartum check-up visit'.

Unit of analysis issues

We intended to include studies where individual postpartum women were randomised and cluster-randomised studies where, for example, the hospital was the unit of randomisation. However, we did not find any related cluster-randomised study. In future updates of this review, for studies that use a cluster-randomised design but did not have any information related to the design effect, we will estimate the design effect based on a fairly large assumed intra-cluster correlation of 0.10. We will base this assumption by analogy on studies about implementation research ([Ukoumunne 1999](#); [Campbell 2000](#)).

Assessment of reporting biases

As only three RCTs met the inclusion criteria, we were unable to construct funnel plots to determine the possibility of publication bias as previously stated in the protocol ([Sothornwit 2015](#)). In future updates of this review, we will construct funnel plots that correspond to the findings of the meta-analysis of the primary outcome that this review needs to address if we identify a sufficient number of included studies (i.e. more than 10). We will also perform sensitivity analyses to investigate the effect on the pooled results of the funnel plots ([Sterne 2011](#)).

Subgroup analysis and investigation of heterogeneity

We did not perform subgroup analyses, as we stated in the Cochrane protocol, due to the limited number of included studies. All included studies were conducted in the USA. In future versions of this review, we will perform subgroup analysis to investigate heterogeneity, if feasible, and we will employ the following methods for subgroup analysis.

- We will consider whether an overall summary is meaningful, and if it is, use a random-effects analysis to produce it.
- We plan to perform subgroup analyses according to age of participants (teenagers versus non-teenagers) and population differences (high-income versus low- and middle-income countries).
- We will assess subgroup differences by interaction tests available within RevMan 5 ([RevMan 2014](#)). We will report the results of subgroup analyses quoting the χ^2 statistic and P value, the interaction test, and I^2 statistic value.

Sensitivity analysis

Only three published RCTs were available for this review, which were at low risk of selection bias. Furthermore, we did not find any unpublished studies. Thus we were unable to perform sensitivity analyses as we stated in the Cochrane protocol ([Sothornwit 2015](#)). In future versions of the review we will perform sensitivity analyses, if feasible, in order to determine the impact of the following factors on effect size.

- Repeating the analysis by excluding unpublished studies (if any).
- Repeating the analysis by excluding trials rated as at 'high' or 'unclear' risk of bias for allocation concealment.



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Interventions for intra-operative pain relief during postpartum mini-laparotomy tubal ligation (Protocol)

Lumbiganon P, Werawatakul Y, Laopaiboon M, Sothornwit J

Lumbiganon P, Werawatakul Y, Laopaiboon M, Sothornwit J.

Interventions for intra-operative pain relief during postpartum mini-laparotomy tubal ligation.

Cochrane Database of Systematic Reviews 2015, Issue 7. Art. No.: CD011807.

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
BACKGROUND	1
OBJECTIVES	2
METHODS	2
ACKNOWLEDGEMENTS	4
REFERENCES	5
APPENDICES	5
CONTRIBUTIONS OF AUTHORS	6
DECLARATIONS OF INTEREST	6
SOURCES OF SUPPORT	6

Interventions for intra-operative pain relief during postpartum mini-laparotomy tubal ligation

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the effectiveness of interventions for pain relief in women undergoing postpartum mini-laparotomy tubal sterilisation.

BACKGROUND

Description of the condition

Postpartum mini-laparotomy tubal ligation (PPTL, see list of abbreviations [Appendix 1](#)) is the most common permanent contraception worldwide ([World contraceptive patterns 2013](#)). Sterilisation is the contraceptive method of choice for 18.9% of all women around the world ([World contraceptive patterns 2013](#)). However the fear of pain during this procedure is an important barrier to receive this operation. Mean intraoperative Numerical Rating Scale (NRS) pain score for PPTL was 5.5, some women required other pain relief interventions or even converted to general anaesthesia (3.75 % of cases) ([Visalyaputra 1999](#)). Pain usually occurs during the following 3 steps: skin incision, peritoneum stretching and tubal ligation.

Description of the intervention

There are many intra-operative pain relief during postpartum tubal ligation including general, regional and local anaesthesia. General and regional anaesthesia are very effective in pain control during PPTL ([Aaronson 2014](#)). However, these interventions require facilities and experienced caregivers that are not widely available. Other possible interventions include injection of anaesthetic agents into mesosalpinx ([Benhamou 1994](#)) or peritoneal instillation ([Ratanalappaiboon 2011](#)), oral administration of Non-Steroidal Anti Inflammatory Drugs (NSAIDs) ([Putland 1999](#)) analgesia and parenteral administration of opioids ([Visalyaputra 1999](#)). These interventions can be performed more easily and do not require highly skilled caregivers. They are more appropriate and practical for low resource settings.

How the intervention might work

Local infiltration of lidocaine before skin incision is adequate only for skin incision pain relief. This is not adequate for pain relief during stretching of peritoneum and pain from ligation on the uterine tubes.

Injection of anaesthetic agents e.g. lidocaine, marcaine into mesosalpinx or peritoneal instillation may inhibit pain by blocking the fast voltage-gated sodium channels in the neuronal cell membrane responsible for signal propagation causing failure transmission of an action potential (Terzlaff 2000). Intravenous or intramuscular injection of NSAIDs can inhibit cyclo-oxygenase-1 (COX-1) and COX-2 enzymes, which are involved in prostaglandin synthesis resulting in their analgesic (Day 2013). Opioids administration can control the pain by being μ (mu) receptor agonists and agonist-antagonists (Trescot 2008). These intervention can prevent pain during peritoneal stretching and ligation of uterine tubes.

Why it is important to do this review

The above mentioned interventions have been widely used in low resource settings due to its simplicity and can be used for outpatient basis. There have been no systematic evaluation about the effectiveness of these interventions. Adequate pain management without regional or general anaesthesia could make this procedure more acceptable to the women who desire sterilisation.

OBJECTIVES

To evaluate the effectiveness of interventions for pain relief in women undergoing postpartum mini-laparotomy tubal sterilisation.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomised controlled trials (RCTs) comparing one intervention to another intervention or placebo or no treatment in this review.

Types of participants

Women undergoing Postpartum mini-laparotomy tubal ligation (PPTL) under local anaesthesia.

Types of interventions

We will consider all interventions for pain relief during and after PPTL including injection of lidocaine to mesosalpinx, intraperitoneal instillation of lidocaine, oral administration of NSAIDs and IM injection of morphine.

Types of outcome measures

Primary outcomes

Pain relief during PPTL evaluated by numerical rating scale (NRS).

Secondary outcomes

1. Adverse effects such as nausea, vomiting, urinary retention or peri-oral numbness.
2. Requirement of regional or general anaesthesia for completing PPTL procedure.

Search methods for identification of studies

Electronic searches

We will search the computerized databases MEDLINE using PubMed, POPLINE, and the Cochrane Central Register of Controlled Trials (CENTRAL), SCOPUS. In addition, we will search for recent clinical trials through ClinicalTrials.gov and the International Clinical Trials Registry Platform (ICTRP). The search strategy is given in [Appendix 2](#).

Searching other resources

We will obtain relevant randomised controlled trials from a search of publications describing pain management for postpartum mini-laparotomy sterilisation. We will search the reference lists of all identified studies for additional, previously unidentified trials. Relevant book chapters and review articles will be searched for all relevant trials.

Data collection and analysis

Selection of studies

Two reviewers, Yuthapong Werawatakul (YW) and Jen Sothornwit (JS) will independently assess the titles and abstracts from our literature search and will evaluate copies of all possibly relevant articles to determine eligibility. Discrepancies will be resolved by discussion or by consulting a third reviewer, Pisake Lumbiganon (PL).

Data extraction and management

Before examining the identified trials for possible inclusion, we will develop and field tested a data collection form, as described in the Cochrane Reviewers' Handbook 5.1 (Higgins 2011). Two reviewers, YW and JS, will independently collect the data on the extraction forms. We will extract the data under unblinded conditions. Discrepancies will be resolved by discussion or by consulting a third reviewer, PL or Malinee Laopaiboon (ML). When necessary we would contact the authors of the trials to seek additional information. Correct entry of the data will be verified by the third reviewer, ML.

Assessment of risk of bias in included studies

Two review authors, YW and JS, will independently assess risk of bias for each included study based on the guidance given in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We will resolve any disagreement by discussion or by consulting PL and ML. Specifically, we will assess the risk of bias in included studies for the following domains.

1) Random sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. We will assess the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We will assess the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

3.1) Blinding of participants and personnel (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results.

We will assess blinding separately for participants and personnel as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

3.2) Blinding of outcome assessment (checking for possible detection bias)

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias

4) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

5) Other bias (checking for bias due to problems not covered by 1) to 4) above)

We will describe for each included study any important concerns we have about other possible sources of bias. We will assess whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

Overall risk of bias

We will make explicit judgements about whether trials are at high risk of bias, according to the criteria given in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We will consider an included trial at low risk of bias if the study will be assessed as at low risk of bias for all domains.

Otherwise, the trial with uncertain risk of bias or with high risk of bias regarding one or more domains will be considered with high risk of bias.

Measures of treatment effect

For dichotomous data such as nausea and vomiting, we will present results as summary risk ratio (RR) with 95% confidence intervals. For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome but use different methods.

Unit of analysis issues

Cluster-randomized trials

Cluster randomized trial is not relevant to this review.

Multi-armed trials

We will include multi-armed trials in the analyses along with individually-randomised trials. We will include the relevant intervention groups in a pair-wise comparison of intervention groups that meet the criteria for including studies in the review. We will combine groups to create a single pair-wise comparison using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomized minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the T^2 , I^2 and χ^2 statistics. We will regard heterogeneity as substantial if I^2 is greater than 30% and either T^2 is greater than zero, or there is a low P value (less than 0.10) in the χ^2 test for heterogeneity.

Assessment of reporting biases

If there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform sensitivity analyses to investigate its effect on the pooled results.

Data synthesis

We will carry out statistical analysis using the Review Manager software (RevMan 2014). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful we will not combine trials. If we use random-effects analyses, the results will be presented as the pooled treatment effect with 95% confidence intervals, and the estimates of T^2 and I^2 .

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will investigate it using subgroup analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it. We plan to carry out the following subgroup analyses.

1. Type of intervention
2. Volume of anaesthetic agent

We plan to do subgroup analysis for pain relief during PPTL outcome.

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2014). We will report the results of subgroup analyses quoting the χ^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We will perform a sensitivity analysis for the primary outcome to explore the effect of trial quality based on concealment of allocation. We will exclude trials rated as 'high risk of bias' or 'unclear risk of bias' for allocation concealment in order to assess for any substantive difference to the overall result.

ACKNOWLEDGEMENTS

none

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* Indicates the major publication for the study

APPENDICES

Appendix I. Abbreviations

COX: Cyclo-Oxygenase

ICTRP: International Clinical Trials Registry Platform

IM: IntraMuscular

NRS: Numerical Rating Scale

NSAIDs: Non-Steroidal Anti Inflammatory Drugs

PPTL: PostPartum mini-laparotomy Tubal Ligation

RCT: Randomised Controlled Trials

RR: Risk Ratio

Appendix 2. Search strategy

PubMed

((sterilization OR tubal ligation OR tubal resection) AND minilaparotomy AND pain), (sterilization OR tubal ligation OR tubal resection) AND postpartum AND pain

CENTRAL

Title, Abstract, Keywords: (sterilization OR tubal ligation OR tubal resection) AND minilaparotomy AND pain
AND Title, Abstract, Keywords: (sterilization OR tubal ligation OR tubal resection) AND postpartum AND pain

POPLINE

All fields: “female sterilization” OR “tubal ligation” OR “tubal resection”

Keyword: minilaparotomy

AND Keyword: pain

EMBASE (Elsevier)

(sterilization OR tubal ligation OR tubal resection) AND minilaparotomy AND postpartum AND pain

Scopus

(sterilization OR tubal ligation OR tubal resection) AND postpartum AND pain

CINAHL Plus with Full Text

(sterilization OR tubal ligation OR tubal resection) AND postpartum AND pain

ClinicalTrials.gov

Intervention: NOT (hysteroscop* OR laparoscop*)

Title acronym/Title: (sterilization OR tubal ligation OR tubal resection) AND pain

ICTRP

Title: pain

Intervention: (sterilization OR tubal ligation OR tubal resection)

CONTRIBUTIONS OF AUTHORS

YW initiated the review topic. YW, JS, PL drafted the protocol. YW, JS, PL and ML reviewed and approved the final version of the protocol.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Faculty of Medicine, Khon Kaen University, Thailand.
- Thai Cochrane Network, Thailand.

External sources

- Thailand Research Fund (Distinguished Professor Award), Thailand.



Cochrane
Library

Cochrane Database of Systematic Reviews

Extended-field irradiation for locally advanced cervical cancer (Protocol)

Thamronganantasakul K, Supakalin N, Kietpeerakool C, Pattanittum P, Lumbiganon P

Thamronganantasakul K, Supakalin N, Kietpeerakool C, Pattanittum P, Lumbiganon P.

Extended-field irradiation for locally advanced cervical cancer.

Cochrane Database of Systematic Reviews 2016, Issue 7. Art. No.: CD012301.

DOI: 10.1002/14651858.CD012301.

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
BACKGROUND	1
OBJECTIVES	2
METHODS	3
ACKNOWLEDGEMENTS	6
REFERENCES	7
APPENDICES	9
WHAT'S NEW	13
CONTRIBUTIONS OF AUTHORS	13
DECLARATIONS OF INTEREST	13
SOURCES OF SUPPORT	14

Extended-field irradiation for locally advanced cervical cancer

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the effectiveness and safety of extended-field irradiation in women with locally advanced cervical cancer.

BACKGROUND

Description of the condition

Cervical cancer is the most common cancer affecting women worldwide, with an estimated 528,000 new cases, and 266,000 cervical cancer deaths, globally in 2012 (GLOBOCAN 2012). Approximately 70% of all cervical cancer cases, and almost 90% of cervical cancer-related deaths occur in developing countries. The high death rate among women residing in developing countries is because most women present with advanced disease (Pisani 1999). A woman's risk of developing cervical cancer before the age of 75 is estimated to range from 0.9% in developed countries to 1.9% in less developed countries (Jemal 2011). This discrepancy in the incidence, risk and stage at diagnosis between developed and developing countries is due to lack of access to effective screening programmes that facilitate early diagnosis and treatment. A summary of the International Federation of Gynecology and Obstetrics (FIGO) staging system for cervical cancer is displayed in

Appendix 1 (FIGO Committee 2014). Patients with FIGO stage Ia1 are normally treated with local excision or simple hysterectomy (surgery to remove the womb and the neck of the womb). FIGO stage Ia2 - Ib1 cervical cancers have an increased risk of pelvic lymph node involvement (3.4% to 15.3%) (Mahawerawat 2013; Sakuragi 1999; Spirtos 2002; Suprasert 2010), and are usually treated with radical hysterectomy (the removal of the womb, the cervix, the upper part of the vagina and the tissues around the cervix), and pelvic lymph node dissection. However, treatment outcomes of pelvic irradiation are comparable to those who undergo surgical treatment (Landoni 1997). Decision-making for early stage of cervical cancer therefore should be tailored based on individual patient characteristics, weighing up the risks of surgery with the longer-term risks of radical radiotherapy. Pelvic irradiation is the principal treatment for more advanced cervical cancer, since the rate of positive pelvic lymph nodes is higher (22.7% to 71.4%) (Marnitz 2005; Sakuragi 1999; Srisomboon 2011; Suprasert 2010), although some recommend extended radical hysterectomy for locally advanced disease (Höckel 2008).

Randomised controlled trial (RCT) data demonstrated that giving chemotherapy at the same time as pelvic irradiation for radiosensitizer, or the so-called “concurrent chemoradiation” significantly improved the rates of local and distant disease control for women with all stages of cervical cancer compared to irradiation alone (Keys 1999; Morris 1999; Peters 2000; Rose 1999; Whitney 1999). Concurrent chemoradiotherapy has been recommended as the treatment of choice instead of pelvic irradiation alone in locally advanced cervical cancer, if clinically feasible (National Cancer Institute 1999). A Cochrane Review also endorsed the use of concurrent chemoradiation versus pelvic irradiation alone for women with cervical cancer based on evidence obtained from individual patient data meta-analysis (CCCMAC 2010).

Description of the intervention

Conventionally, whole pelvis external-beam irradiation treatment field covers the space between L4 (fourth lumbar spine) to L5 (fifth lumbar spine) to the mid of pubis, or to a line 4 cm below the most distal vaginal or cervical site of disease. Lateral fields are designed to encompass S3 (third sacral spine) posteriorly, with a margin of at least 3 cm from the primary cervical tumour. The radiation schedule is about 1.6 to 2.0 Gy (unit of irradiation dose) per day, five days per week, with a total radiation dose of 45 to 50 Gy. The prescribed dose is delivered to the mid-depth on the central axis of the beams. Intracavitary brachytherapy is performed after the completion of pelvic radiotherapy and a total cumulative dose to point A is at least 80 Gy (Eifel 2004; Lim 2011; Rotman 1978; Rotman 1990).

Extended-field or para-aortic irradiation is the extension of whole pelvis external beam irradiation to also cover the para-aortic lymph nodes (the nodes lying adjacent to the aorta, the major vessel in the abdomen). This additional irradiation is delivered in the same setting with the conventional whole pelvis external-beam irradiation. The irradiation schedule and total dose of the two interventions are the same, but the extended-field irradiation covers a wider area (Eifel 2004; Rotman 1978; Rotman 1990).

Severe acute and late morbidities (side effects and complications of treatment) seem to be fundamental reasons limiting the use of extended-field irradiation for cervical cancer, particularly among women receiving chemoradiation. Severe acute and late toxicities (≥ 3 grade) in women who had undergone extended-field irradiation with concomitant chemotherapy occur at approximately 33% to 80% and 10% to 15%, respectively (Kim 2009; Sood 2003; Varia 1998). Approximately 10% and 6% of women receiving extended-field irradiation develop severe acute and late toxicities, respectively following extended-field irradiation alone (Sood 2003).

How the intervention might work

Occult para-aortic lymph node disease can occur in women thought to have locally advanced cervical cancer, which is confined to the pelvis. From a previous literature review, which was undertaken to evaluate the impact of pretreatment surgical para-aortic lymph node staging on treatment outcomes of cervical cancer, para-aortic lymph node metastasis were noted in 11% of women with stage I disease, 13% to 16% with stage II, 29% with stage III, and 36% with stage IVA (Smits 2014). In one review of the literature, despite having normal findings on positron emission tomography (PET) or positron emission tomography-computed tomography (PET-CT), 4% to 15% of women, thought to have negative para-aortic lymph node on PET and PET-CT, were found to have para-aortic lymph node metastasis (Smits 2014).

Standard radical pelvic irradiation may be inadequate for patients with para-aortic lymph node metastasis, since the para-aortic area is outside of standard fields of traditional pelvic irradiation techniques. Para-aortic lymph node recurrence is a frequent cause of extrapelvic failure among women with locally advanced cervical cancer who had undergone standard technique of pelvic radiation (21.6% to 57.1%) (Hong 2004; Sakurai 2001). Even in the era of concurrent chemoradiation, para-aortic lymph node metastasis has been noted in approximately 7% to 15% of women undergoing concurrent chemoradiation for cervical cancer (Eifel 2004; Pearcey 2002; Toita 2012).

Previous studies have observed that extended-field irradiation prolonged the survival of women with endometrial cancer (Rose 1992) and cervical cancer (Marnitz 2015; Varia 1998) who have para-aortic lymph node metastasis. In addition, prophylaxis extended-field irradiation to the para-aortic region improved overall survival in women with cervical cancer (Rotman 1995). Based on these findings, delivering extended-field irradiation to cover para-aortic regions aimed to eliminate unrecognised metastatic lesion might be effective for reducing treatment failure at this region and thus improving treatment outcomes of women with cervical cancer.

Why it is important to do this review

The outcome for women with recurrent cervical cancer is poor and para-aortic lymph node recurrence is one of the common sites of treatment failure in cervical cancer patients. However, there is significant morbidity from extended-field irradiation. Evidence for an effective strategy in reducing para-aortic lymph node recurrence is therefore required. Although there is a theoretical possibility in that extended-field irradiation might decrease the risk of para-aortic recurrence, to date there has been no systematic review evaluating the impact of extended-field irradiation on the treatment outcomes of women with locally advanced cervical cancer.

OBJECTIVES

To evaluate the effectiveness and safety of extended-field irradiation in women with locally advanced cervical cancer.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs). We will not include quasi-randomised trials as these may have been subjected to bias.

Types of participants

Women aged 18 years or older undergoing first-line treatment for locally advanced cervical cancer. Cervical cancers with the largest diameter equal or larger than 4 cm and/or FIGO stage IIB to IVA are considered locally advanced. Details of the FIGO staging classification of cervical cancer are shown in [Appendix 1 \(FIGO Committee 2014\)](#).

Types of interventions

We will compare extended-field versus standard radical irradiation technique as follows.

- Extended-field irradiation versus standard radical irradiation technique alone.
- Extended-field irradiation versus standard radical irradiation technique given concurrently with chemotherapy.
- Extended-field irradiation versus standard radical irradiation technique in conjunct with chemotherapy.

Types of outcome measures

Primary outcomes

- Overall survival (OS): Survival until death from all causes. Survival will be assessed from the time when women are enrolled in the study.
- Para-aortic lymph node recurrence: Any relapse or persistent disease at the para-aortic region.

Secondary outcomes

- Progression-free survival (PFS) or disease progression: Survival until appearance of a new lesion. Survival will be assessed from the time when women are enrolled in the study.
- Non-para-aortic recurrence: Recurrent disease other than the para-aortic region will be classified as locoregional and distant recurrences.
- Adverse events which will be classified as: (A) Acute complications including digestive complications (e.g. nausea/vomiting, diarrhoea); urological complications (e.g. cystitis); haematological complications (e.g. anaemia, leukopenia, neutropenia, and thrombocytopenia); and cardiovascular and thromboembolic complications (e.g. myocardial infarction, arterial thrombosis, venous thrombosis, pulmonary embolism). (B) Late complications including digestive complications (e.g. proctitis, sigmoiditis, intestinal obstruction, and fistular formation); and urological complications (e.g. chronic cystitis, incontinence, ureteral stenosis, and fistula).
- Quality of life (QoL): using validated scales i.e. European Organization for Research and Treatment of Cancer (EORTC) QLQ-CX24 ([Greimel 2006](#)).
- Cost-effectiveness: using a scale that has been validated and reported in a peer-reviewed publication i.e. European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) ([Cherny 2015](#)).

We will present a 'Summary of findings table' reporting the following outcomes listed in order of priority (see [Data synthesis](#)).

- Overall survival.
- Progression-free survival.
- Para-aortic lymph node recurrence.
- Non-para-aortic recurrence.
- Adverse events.
- Quality of life.
- Cost-effectiveness.

Search methods for identification of studies

Electronic searches

We will search the following electronic databases.

- Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library, latest issue).
- MEDLINE (1946 to present date).
- Embase (1980 to present date).

The Ovid MEDLINE search strategy is presented in [Appendix 2](#). For databases other than MEDLINE, we will adapt the search strategy accordingly.

Searching other resources

Ongoing studies and Grey literature

We will search the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (<http://www.who.int/ictcp/en/>) and ClinicalTrials.gov to identify any ongoing trials. If ongoing trials that have not been published are identified, we will approach the principal investigators, and major co-operative groups active in this area, to ask for relevant data. We will search the following databases for grey literature: Open-Grey (<http://www.opengrey.eu/>) and Index to theses (ProQuest Dissertations & Theses: UK & Ireland).

Handsearching

We will handsearch the citation lists of included studies, key textbooks, and previous systematic reviews and contact experts in the field to identify further reports of trials. We will also handsearch the reports of conferences in the following sources.

- Annual Meeting of the American Society of Gynecologic Oncologist.
- Annual Meeting of the American Society of Radiation Oncology (ASTRO).
- Annual Meeting of European Society of Radiotherapy and Oncology (ESTRO).
- Annual Meeting of European Society of Medical Oncology (ESMO).
- Annual Meeting of the American Society of Clinical Oncology (ASCO).
- Annual Meeting of the British Gynaecological Cancer Society (BGCS).
- Biennial Meeting of the Asian Society of Gynecologic Oncology (ASGO).
- Biennial Meeting of Asia and Oceania Federation of Obstetrics and Gynaecology (AOFOG).
- Biennial Meeting of the European Society of Gynaecologic Cancer (ESGO).
- Biennial Meeting of the International Gynecologic Cancer Society (IGCS).

Data collection and analysis

Selection of studies

We will download all titles and abstracts retrieved by electronic searching to a reference management database ([Endnote](#)). After duplicates are removed, we will transfer these data to Covidence (<https://www.covidence.org/>). Two review authors (KT and NS) will examine the remaining references independently. We will exclude those studies which clearly do not meet the inclusion criteria, and

we will obtain copies of the full-text of potentially relevant references. Two review authors (KT and NS) will independently assess the eligibility of the retrieved reports/publications. We will resolve any disagreement through discussion or, if required, we will consult a third review author (CK). We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will use the details regarding the selection process in Covidence to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table ([Liberati 2009](#)).

Data extraction and management

Two review authors (KT and NS) will independently extract study characteristics and outcome data from included studies using Covidence. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third review author (PL or CK). One review author (PP) will transfer data from Covidence into the Review Manager ([RevMan 2014](#)). A second review author (CK) will check study characteristics for accuracy against the trial report.

For included studies, we will extract the following data.

- Author, year of publication and journal citation (including language).
- Country.
- Setting.
- Inclusion and exclusion criteria.
- Study methodology.
- Study population and characteristics:
 - total number enrolled;
 - patient characteristics;
 - age;
 - co-morbidities;
 - other baseline characteristics;
 - FIGO stage of cervical cancer;
 - tumour size (largest diameter);
 - histopathological type of cervical cancer;
 - status of para-aortic lymph node.
- Intervention details
 - any regimens of pelvic irradiation or concurrent chemoradiation plus extended-field irradiation;
 - irradiation technique;
 - dose;
 - duration;
 - schedule.
- Comparison
 - any regimens of pelvic irradiation or concurrent chemoradiation.
- Risk of bias in study (see below).
- Duration of follow-up.

- Outcomes: For each outcome, we will extract the outcome definition and unit of measurement (if relevant). For adjusted estimates, we will record variables adjusted for in analyses.
- Results: We will extract the number of participants allocated to each intervention group, the total number analysed for each outcome, and the missing participants.
- Notes: Funding for trial, and notable conflicts of interest of trial authors.

Results will be extracted as follows.

- For time to event data (survival and disease progression), we will extract the log of the hazard ratio [log(HR)] and its standard error (SE) from trial reports. If these are not reported, we will attempt to estimate the log (HR) and its SE using the methods of [Parmar 1998](#).
- For dichotomous outcomes (e.g. adverse events or deaths, if it is not possible to use the HR), we will extract the number of patients in each treatment arm who experienced the outcome of interest and the number of patients assessed at endpoint, in order to estimate a risk ratio (RR).
- For continuous outcomes (e.g. QoL measures), we will extract the final value and standard deviation (SD) of the outcome of interest and the number of patients assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference between treatment arms.

Where possible, all data extracted will be those relevant to an intention-to-treat analysis, in which participants will be analysed in groups to which they were assigned.

Assessment of risk of bias in included studies

We will assess and report on the methodological quality and risk of bias in included studies in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)), which recommends the explicit reporting of the following individual elements for RCTs.

- Selection bias: random sequence generation and allocation concealment.
- Performance bias: blinding of participants and personnel (patients and treatment providers).
- Detection bias: blinding of outcome assessment.
- Attrition bias: incomplete outcome data.
- Reporting bias: selective reporting of outcomes.
- Other possible bias.

Two review authors (NS and CK) will independently apply the 'Risk of bias' tool and differences will be resolved by discussion or by appeal to a third review author (PL). We will judge each item as being at high, low or unclear risk of bias as set out in the criteria displayed in [Appendix 3](#) ([Higgins 2011](#)). We will provide a quote from the study report and/or a statement as justification for the judgement for each item in the 'Risk of bias' table. We will summarise results in both a 'Risk of bias' graph and a 'Risk

of bias' summary. When interpreting treatment effects and meta-analyses, we will take into account the risk of bias for the studies that contribute to that outcome. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the table.

Measures of treatment effect

We will use the following measures of the effect of treatment.

- For survival outcomes (e.g. overall and progression-free survivals), we will use the HR and 95% confidence interval (CI).
- For dichotomous outcomes (e.g. adverse events, recurrences, and death), we will analyse data based on the number of events and the number of people assessed in the intervention and comparison groups. We will use these to calculate the RR and 95% CI.
- For continuous outcomes (e.g. quality of life and cost-effectiveness measures), we will analyse data based on the mean, SD and number of people assessed for both the intervention and comparison groups to calculate mean difference (MD) between treatment arms with a 95% CI. If the MD is reported without individual group data, we will use this to report the study results. If more than one study measures the same outcome using different tools, we will calculate the standardised mean difference (SMD) and 95% CI using the inverse variance method.

Unit of analysis issues

We will include studies where individual patients were randomised and cluster-randomised studies (CRT). For studies that used a cluster-randomised design but do not have any information related to the design effect, we will estimate the design effect based on a fairly large assumed intra-cluster correlation of 0.10. We will base this assumption by analogy on studies about implementation research ([Campbell 2000](#); [Ukoumunne 1999](#)). We will follow the methods stated in the *Cochrane Handbook for Systematic Reviews of Interventions* for determining the calculations ([Higgins 2011](#)). In a study with multiple intervention groups, where possible, we will combine all relevant experimental intervention groups into a single group to create a single pair-wise comparison ([Higgins 2011](#)).

Dealing with missing data

We will not impute missing outcome data for any of the outcomes.

Assessment of heterogeneity

Heterogeneity will be clinically assessed by visual inspection of the forest plots. We will also assess statistical heterogeneity in each meta-analysis using the I^2 statistic and χ^2 test ([Higgins 2003](#)). We will regard heterogeneity as substantial if the I^2 statistic value is greater than 50%, or there is a low P value (< 0.10) in the χ^2 test

for heterogeneity (Deeks 2001; Higgins 2011). If there is substantial statistical heterogeneity, we will carry out subgroup analyses to assess differences between the included studies. However, if there is clinical, methodological or considerable statistical heterogeneity (I^2 greater than 75%) across included studies (Higgins 2011), we will not report pooled results from meta-analysis, but will instead use a narrative approach to data synthesis.

Assessment of reporting biases

We will examine funnel plots corresponding to meta-analysis of the primary outcome to assess the potential for small-study effects such as publication bias if more than 10 studies are identified. We plan to assess funnel plot asymmetry visually, and if asymmetry of funnel plots is identified we will perform exploratory analyses to investigate it. (Sterne 2011).

Data synthesis

If feasible, we will pool the results in meta-analyses. We will use the random-effects model with inverse variance weighting for all meta-analyses (DeSimonian 1986). We will perform statistical analysis using RevMan 2014.

- For time-to-event data, we will pool HRs using the generic inverse variance.
- For any dichotomous outcomes, we will calculate the RRs for each study and these will then be pooled.
- For continuous outcomes, will pool the MDs between the treatment arms, if all trials measure the outcome on the same scale; otherwise we will pool SMDs.

We will prepare a 'Summary of findings' table to display the results of the meta-analysis, based on the methods described in chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011). We will present the results of the meta-analysis for the outcomes, and harms, as outlined in the [Types of outcome measures](#) section. If we are unable to pool the results using meta-analysis methods, we will conduct a narrative review of the available results.

Main outcomes of 'Summary of findings' table for assessing the quality of the evidence

We will present the overall quality of the evidence for each outcome according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which takes into account issues not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias), but also to external validity such as directness of results (Langendam 2013). We will create a 'Summary of findings' table (Appendix 4) based on the methods described the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and using GRADEpro GDT. We

will use the GRADE checklist and GRADE Working Group quality of evidence definitions (Meader 2014). We will downgrade the evidence from 'high' quality by one level for serious (or by two for very serious) for each limitation.

- **High quality:** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

We will carry out subgroup analysis for the following factors.

- Type of treatment (concurrent chemoradiation versus radiation only).
- Status of para-aortic lymph node (unknown versus negative on radiological imaging).

We will assess subgroup differences by interaction tests available within Review Manager (RevMan 2014). We will report the results of subgroup analyses quoting the χ^2 statistic and P value, the interaction test, and I^2 statistic value.

Sensitivity analysis

We will perform sensitivity analysis in order to assess the effect of the following factors.

- Repeating the analysis excluding unpublished studies (if any).
- Repeating the analysis excluding studies judged to be at "high" or "unclear" risk of bias for allocation concealment.

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* Indicates the major publication for the study

APPENDICES

Appendix I. Staging classification of cervical cancer

FIGO Stage			Description
I			The carcinoma is confined to the cervix.
	IA		Invasive cancer identified only microscopically. (All gross lesions even with superficial invasion are Stage IB cancers.) Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm
		IA1	Measured invasion of stroma ≤ 3 mm in depth and ≤ 7 mm width
		IA2	Measured invasion of stroma > 3 mm and < 5 mm in depth and ≤ 7 mm width
	IB		Clinical lesions confined to the cervix, or preclinical lesions greater than stage IA
		IB1	Clinical lesions no greater than 4 cm in size.
		IB2	Clinical lesions > 4 cm in size.
II			The carcinoma extends beyond the uterus, but has not extended onto the pelvic wall or to the lower third of vagina
	IIA		Involvement of up to the upper 2/3 of the vagina. No obvious parametrial involvement
		IIA1	Clinically visible lesion ≤ 4 cm.
		IIA2	Clinically visible lesion > 4 cm.
	IIB		Parametrial involvement but not onto the pelvic sidewall.
III			The carcinoma has extended onto the pelvic sidewall. On rectal examination, there is no cancer free space between the tumour and pelvic sidewall. The tumour involves the lower third of the vagina. All cases of hydronephrosis or non-functioning kidney should be included unless they are known to be due to other causes
	IIIA		Involvement of the lower vagina but no extension onto pelvic sidewall
	IIIB		Extension onto the pelvic sidewall, or hydronephrosis/non-functioning kidney
IV			The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum
	IVA		Spread to adjacent pelvic organs.

(Continued)

	IVB	Spread to distant organs.

Appendix 2. MEDLINE Ovid search strategy

1. Uterine Cervical Neoplasms/
2. (cervi* adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*)).mp.
3. 1 or 2
4. exp Radiotherapy/
5. radiotherap*.mp.
6. (irradiat* or radiat*).mp.
7. radiotherapy.fs.
8. 4 or 5 or 6 or 7
9. (para-aortic or paraaortic or peri-aortic or periaortic).mp.
10. extended field.mp.
11. 9 or 10
12. 3 and 8 and 11
13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. randomized.ab.
16. placebo.ab.
17. clinical trials as topic.sh.
18. randomly.ab.
19. trial.ab.
20. 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 12 and 20

Key:

[mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

Appendix 3. 'Risk of bias' assessment

Assessment of risk of bias will be based on chapter 8 of [Higgins 2011](#):

- Random sequence generation
 - Low risk of bias e.g. participants assigned to treatments on the basis of a computer-generated random sequence or a table of random numbers
 - High risk of bias e.g. participants assigned to treatments on the basis of date of birth, clinic id-number or surname, or no attempt to randomise participants
 - Unclear risk of bias e.g. not reported, information not available
- Allocation concealment
 - Low risk of bias e.g. where the allocation sequence could not be foretold
 - High risk of bias e.g. allocation sequence could be foretold by patients, investigators or treatment providers
 - Unclear risk of bias e.g. not reported.
- Blinding of participants and personnel
 - Low risk of bias if participants and personnel were adequately blinded
 - High risk of bias if participants were not blinded to the intervention that the participant received
 - Unclear risk of bias if this was not reported or unclear
- Blinding of outcomes assessors
 - Low risk of bias if outcome assessors were adequately blinded

- High risk of bias if outcome assessors were not blinded to the intervention that the participant received
- Unclear risk of bias if this was not reported or is unclear
- Incomplete outcome data: we will record the proportion of participants whose outcomes were not reported at the end of the study. We will code a satisfactory level of loss to follow-up for each outcome as:
 - Low risk of bias e.g. if fewer than 20% of participants were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms
 - High risk of bias e.g. if more than 20% of participants were lost to follow-up or reasons for loss to follow-up differed between treatment arms
 - Unclear risk of bias e.g. if loss to follow-up was not reported
- Selective reporting of outcomes
 - Low risk of bias e.g. review reports all outcomes specified in the protocol
 - High risk of bias e.g. the study is suspected that outcomes have been selectively reported
 - Unclear risk of bias e.g. it is unclear whether outcomes have been selectively reported
- Other bias
 - Low risk of bias e.g. the review authors do not suspect any other source of bias and the trial appears to be methodologically sound
 - High risk of bias e.g. the review authors suspect that the trial was prone to an additional bias
 - Unclear risk of bias e.g. the review authors are uncertain whether an additional bias may have been present

Appendix 4. 'Summary of findings' table template

Title: Extended-field irradiation for locally advanced cervical cancer						
Patient or population: Women undergoing first-line treatment for locally advanced cervical cancer						
Settings: specialist hospital						
Intervention: extended-field irradiation						
Comparison: radical irradiation technique with or without chemotherapy						
Outcomes	Illustrative comparative risks*		Relative effect (95% CI)	No of participants (studies)	Quality of evidence (GRADE)	Comment
	Assumed risk	Corresponding risk				
1 Overall survival						
2 Para-aortic lymph node recurrence						
3 Progression free survival						
4 Non-para-aortic recurrence						
5 Adverse events						

(Continued)

6 Quality of life						
7 Cost-effective-ness						
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; HR: hazard ratio; MD: mean difference; RR: risk ratio; OR: odds ratio GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.						

WHAT'S NEW

Date	Event	Description
8 August 2016	Amended	Text amendments.

CONTRIBUTIONS OF AUTHORS

Narudom Supakalin: conceived the review question, developed, co-ordinated and completed the protocol

Komsan Thamronganantasakul: conceived the review question, developed and completed the protocol

Chumnan Kietpeerakool: conceived the review question, developed, co-ordinated and completed the protocol

Porjai Pattanittum: editing and advisory role

Pisake Lumbiganon: developed and co-ordinated the development of the protocol, editing and advisory role

DECLARATIONS OF INTEREST

Narudom Supakalin: none known

Komsan Thamronganantasakul: none known

Chumnan Kietpeerakool: none known

Porjai Pattanittum: none known

Pisake Lumbiganon: none known

SOURCES OF SUPPORT

Internal sources

- Department of Obstetrics and Gynaecology, Faculty of Medicine, Khon Kaen University, Thailand.
- Department of Radiology, Faculty of Medicine, Khon Kaen University, Thailand.
- Department of Biostatistics and Demography, Faculty of Public Health, Khon Kaen University, Thailand.
- Cochrane Thailand, Thailand.

External sources

- Thailand Research Fund (Distinguished Professor Award), Thailand.



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Simple versus radical hysterectomy with pelvic lymphadenectomy for women with stage IA2-IB1 cervical cancer (Protocol)

Supoken A, Kietpeerakool C, Laopaiboon M, Lumbiganon P

Supoken A, Kietpeerakool C, Laopaiboon M, Lumbiganon P.

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
BACKGROUND	1
OBJECTIVES	2
METHODS	2
ACKNOWLEDGEMENTS	6
REFERENCES	7
APPENDICES	9
CONTRIBUTIONS OF AUTHORS	12
DECLARATIONS OF INTEREST	12
SOURCES OF SUPPORT	12

Simple versus radical hysterectomy with pelvic lymphadenectomy for women with stage IA2-IB1 cervical cancer

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To determine the effectiveness and adverse effects of simple hysterectomy, performed with pelvic lymphadenectomy, for women with stage IA2-IB1 cervical cancer.

BACKGROUND

Description of the condition

Persistent infection with high-risk or oncogenic subtypes of human papillomavirus is the primary cause of cervical cancer (Clifford 2003). According to the Global Cancer Statistics, 2012 the incidence of cervical cancer is on the decline, largely due to effective screening programmes. However, it remains an important public health problem for women, especially in less economically developed countries (Torre 2015). Worldwide, cervical cancer is the fourth most commonly diagnosed cancer affecting women (527,600 new cases in 2012), after breast, colorectal and lung cancers, respectively. It is also the fourth most common cause of cancer death (265,700 deaths) (Ferlay 2015; Torre 2015). In less

economically developed countries, cervical cancer is the second most common cancer among women after breast cancer. Approximately 90% of cervical cancer-related deaths are in developing countries, which reflects the failure either to initiate or sustain effective cervical cancer prevention programmes in these countries (Ferlay 2015; Torre 2015).

Treatment of cervical cancer depends on the stage of disease. Information for staging of cervical cancer, including tumour size and spread, is still largely based on clinical staging following an examination under anaesthetic, to palpate the cervix and supporting structures, as well as a cystoscopy and sigmoidoscopy, to examine for bladder or bowel involvement (see Appendix 1 for the International Federation of Gynecology and Obstetrics (FIGO) staging for carcinoma of the cervix). In most more economically developed countries clinical staging will be augmented by imaging, including magnetic resonance imaging (MRI) and computerised

tomography (CT) scans, to look for local and distant disease extent, and increasingly positron emission tomography (PET) scans are used to more accurately determine distant disease spread prior to planned radical treatment.

Description of the intervention

A simple hysterectomy is the type of operation commonly performed for benign conditions, such as menorrhagia, as well as endometrial (womb lining) cancer. In a simple hysterectomy the uterine vessels (blood supply to the uterus/womb) are divided close to the side of the uterine body (womb) and neck of the womb (cervix), often shaving into the cervical tissues (Querleu 2008). This is done to avoid damage to the ureters (tubes that take urine from the kidneys to the bladder), which run around the side of the cervix as they travel into the bladder. A radical hysterectomy involves removing the womb, cervix and a cuff of vaginal tissue, as well as the tissue around the cervix and upper vagina called the parametria. The parametria is where the blood vessels and lymphatic supply to the cervix and womb run, where the ureters curve around the cervix/vagina, where the nerves controlling the bladder pass through, and the route through which cervical cancer may spread. For cervical cancer stage IA2-IB1, pelvic lymphadenectomy (bilateral pelvic lymph node dissection, which is the surgical removal of the lymph glands found in the pelvis) is performed along with hysterectomy to assess pelvic node metastasis. Radical hysterectomy with pelvic lymphadenectomy is the standard surgical procedure for stage IA2-IB1 cervical cancer, if preservation of fertility is not desired (Verleye 2009). The survival outcomes of women undergoing radical hysterectomy with pelvic lymphadenectomy for stage IA2-IB1 cervical cancer is excellent, with an estimated overall five-year survival of approximately 90% (Kim 2000; Mahawerawat 2013; Srisomboon 2011; Suprasert 2010).

However, because the ureters and the nerves that supply the bladder run through the parametrial area, these structures are at risk of damage during a radical hysterectomy. This explains why there are additional and increased risks following a radical hysterectomy compared to a simple hysterectomy. These include ureteric damage, fistula formation, and bladder and bowel denervation, leading to urinary retention and voiding problems (i.e. difficulty in emptying bladder (micturition), urinary hesitancy and recurrent urinary tract infections due to urinary retention), which may be short-lived or long-term problems (Landoni 2012; Ralph 1991). Preservation of parametrium during simple hysterectomy could minimise damage to adjacent organs, pelvic autonomic nerves and vascular supply, thus resulting in a less morbidity compared to radical hysterectomy (Landoni 2012). However, this could lead to under-treatment, with a potential increased need for radiotherapy (and its long-term complications), risk of disease recurrence and reduced survival.

How the intervention might work

The rate of parametrial spread of cancer in early-stage cervical cancer varies from less than 1% to up to 10% (Covens 2002; Frumovitz 2009; Kamimori 2011; Kato 2015; Kodama 2011; Steed 2006; Stegeman 2007). The size of the cervical tumour is the strongest preoperative factor predicting parametrial invasion and previous studies have shown that parametrial involvement occurs in fewer than 1% to 1.9% of women with a cervical lesion of 20 mm or less (Covens 2002; Kamimori 2011; Kato 2015; Steed 2006).

Acknowledging that there is a relatively low risk of parametrial involvement in a selected group of women with early-stage cervical cancer, carrying out a simple hysterectomy, in conjunction with pelvic lymphadenectomy, might be more appropriate for women with clinical stage IA2-IB1 cervical cancer. The apparent advantage of simple hysterectomy over radical hysterectomy is potentially a reduced risk of surgically related short and long-term complications.

Why it is important to do this review

Tailoring surgical treatment is a fundamental factor in planning modern cancer surgery and cervical cancer is no exception. Although the aim of treatment for early-stage cervical cancer is undoubtedly curative, the potential for treatment-related complications and adverse effects on quality of life should be taken into consideration when planning treatment options.

Radical hysterectomy is associated with high complication rates, particularly micturition and urinary tract injury, which occur in 5.1% to 31.0% and 0.5% to 1.3% of women, respectively (Alexander-Sefre 2006; Charoenkwan 2007; Jensen 2004a; Kietpeerakool 2008; Suprasert 2010). Considering the low rate of parametrial spread, simple hysterectomy, performed in conjunction with pelvic lymphadenectomy, may be effective for a selected group of women with stage IA2-IB1 cervical cancer. To our knowledge, there are no systematic reviews evaluating the effectiveness of simple hysterectomy for women with stage IA2-IB1 cervical cancer.

OBJECTIVES

To determine the effectiveness and adverse effects of simple hysterectomy, performed with pelvic lymphadenectomy, for women with stage IA2-IB1 cervical cancer.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs). If no RCTs are identified we will include non-randomised studies (NRS) with a parallel comparison, i.e. non-randomised controlled trials, cohort and case-control studies. We will only include NRS that have analysed results for intervention effects adjusted for baseline characteristics.

Types of participants

Women aged 18 years or over with FIGO stage IA2-IB1 cervical cancer. Details of the staging classification of cervical cancer are shown in [Appendix 1 \(FIGO Committee 2014\)](#).

Types of interventions

We will include trials comparing simple hysterectomy (type I) with pelvic lymphadenectomy versus radical hysterectomy with pelvic lymphadenectomy for cervical cancer stage IA2-IB1.

Types of outcome measures

Primary outcomes

- Overall survival (OS): survival until death from all causes. Survival will be assessed from the time when women are enrolled in the study.
- Disease-free survival (DFS): survival until the appearance of a new lesion of disease. Survival will be assessed from the time when women are enrolled in the study.

Secondary outcomes

- Adverse events:
 - febrile morbidity;
 - surgical site infections;
 - genitourinary complications (e.g. fistula, bladder dysfunction, hydronephrosis, vaginal stenosis);
 - gastrointestinal complications (e.g. fistula, constipation; lymphovascular complications (e.g. lymphocyst, lymphoedema, thrombosis, embolism);
 - direct surgical morbidity (e.g. injury to bladder, ureter, small bowel or colon);
 - postoperative complication (e.g. re-operation (an operation to correct a condition not corrected by a previous operation or to correct the complications of a previous operation);
 - readmission (a hospitalisation that occurs shortly after a discharge, which is most often measured as within 30 days but

it could be shorter or longer. Such readmissions are often but not always related to a problem inadequately resolved in the prior hospitalisation);

- blood component transfusion (the transfer of blood or blood components from one person (the donor) into the bloodstream of another person (the recipient)).

We will categorise the severity of adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE 2010).

- Sexual dysfunction: using a validated scale, i.e. Sexual function-Vaginal change Questionnaire (SVQ) ([Jensen 2004b](#)).
- Cost-effectiveness: using a validated scale, i.e. European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) ([Cherny 2015](#)).
- Quality of life: using a scale that has been validated through reporting of norms in a peer-reviewed publication, i.e. European Organization for Research and Treatment of Cancer (EORTC) QLQ-CX24 cervical cancer-specific quality of life questionnaire ([Greimel 2006](#)).

We will present a 'Summary of findings' table reporting the following outcomes listed in order of priority (see [Data synthesis](#)):

1. Overall survival
2. Disease-free survival
3. Rate of adverse events
4. Sexual dysfunction
5. Cost-effectiveness
6. Quality of life

Search methods for identification of studies

We will include either RCTs or NRS, irrespective of the language of publication, publication status or sample size.

Electronic searches

We will search the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL, latest issue);
- MEDLINE (1946 to present date);
- Embase (1980 to present date).

The Ovid MEDLINE search strategy is presented in [Appendix 2](#). For databases other than MEDLINE, we will adapt the search strategy accordingly.

All relevant articles will be identified on PubMed and we will make a further search for newly published articles using the 'related articles' feature.

Searching other resources

Ongoing trials and grey literature

We will search the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (<http://www.who.int/ictcp/en/>) and ClinicalTrials.gov to identify any ongoing trials. If ongoing trials that have not been published are identified, we will approach the principal investigators and major co-operative groups active in this area, to ask for relevant data. We will search the following databases for grey literature: Open Grey (<http://www.opengrey.eu/>) and Index to Theses (ProQuest Dissertations & Theses: UK & Ireland).

Handsearching

We will handsearch the citation lists of included studies, key textbooks and previous systematic reviews, and we will contact experts in the field to identify further reports of trials. We will also hand-search the reports of conferences in the following sources:

- Annual Meeting of the American Society of Gynecologic Oncologists;
- Annual Meeting of the International Gynecologic Cancer Society;
- Annual Meeting of the European Society of Medical Oncology (ESMO);
- Annual Meeting of the American Society of Clinical Oncology (ASCO);
- Annual Meeting of the British Gynaecological Cancer Society (BGCS);
- Biennial Meeting of the Asian Society of Gynecologic Oncology (ASGO);
- Biennial Meeting of the Asia and Oceania Federation of Obstetrics and Gynaecology (AOFOG);
- Biennial Meeting of the European Society of Gynaecologic Cancer (ESGO); and
- Biennial Meeting of the International Gynecologic Cancer Society (IGCS).

Data collection and analysis

Selection of studies

We will download all titles and abstracts retrieved by electronic searching to a reference management database (EndNote). After duplicates are removed, we will transfer these data to *Covidence* (<https://www.covidence.org/>). Two review authors (AS and CK) will examine the remaining references independently. We will exclude those studies that clearly do not meet the inclusion criteria and we will obtain copies of the full text of potentially relevant references. Two review authors (AS and CK) will independently

assess the eligibility of the retrieved reports/publications. We will resolve any disagreement through discussion or, if required, we will consult a third person (PL). We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will use the details regarding the selection process in *Covidence* to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Liberati 2009).

Data extraction and management

Two review authors (AS and CK) will independently extract study characteristics and outcome data from included studies using *Covidence*. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third person (PL). One review author (ML) will transfer data from *Covidence* into Review Manager (RevMan 2014).

For included studies, we will extract the following data:

- Author, year of publication and journal citation (including language)
- Country
- Setting
- Inclusion and exclusion criteria
- Study design and methodology
- Study population and disease characteristics
 - Total number enrolled
 - Participant characteristics
 - Age
 - Co-morbidities
 - Other baseline characteristics
 - Surgical technique (laparotomy, laparoscopy or robotic-assisted procedure)
 - Stage of cervical cancer (IA2 or IB1)
 - Histopathological subtype of cervical cancer
 - Tumour size (largest tumour diameter)
 - Lymphadenectomy details including technique (sampling versus complete dissection) and status of lymph nodes (negative or positive for metastasis)
- Intervention details
 - Simple hysterectomy or type I hysterectomy
- Comparison
 - Type II or type III hysterectomy
- Risk of bias in study (see below)
- Duration of follow-up
- Outcomes: for each outcome, we will extract the outcome definition and unit of measurement (if relevant). For adjusted estimates, we will record variables adjusted for in analyses.
- Results: we will extract the number of participants allocated to each intervention group, the total number analysed for each outcome and the missing participants.

- Notes: funding for trial and notable conflicts of interest of trial authors.

We will extract results as follows:

- For time-to-event data (survival outcomes), we will extract the log of the hazard ratio (log(HR)) and its standard error from trial reports. If these are not reported, we will attempt to estimate the log(HR) and its standard error using the methods of [Parmar 1998](#).
- For dichotomous outcomes (e.g. adverse events or deaths) we will extract the number of women in each treatment arm who experienced the outcome of interest and the number of women assessed at endpoint, in order to estimate a risk ratio (RR).
- For continuous outcomes (e.g. quality of life measures), we will extract the final value and standard deviation of the outcome of interest and the number of women assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference between treatment arms (if trials measured outcomes on the same scale) or standardised mean difference (if trials measured outcomes on different scales) between treatment arms and its standard error.

Where possible, all data extracted will be those relevant to an intention-to-treat analysis, in which participants will be analysed in the groups to which they were assigned. In a study with multiple intervention groups, we will combine all relevant experimental intervention groups into a single group to create a single pair-wise comparison ([Higgins 2011](#)).

Assessment of risk of bias in included studies

We will assess and report on the methodological quality and risk of bias of included studies in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)), which recommends the explicit reporting of the following individual elements for RCTs:

- Selection bias: random sequence generation and allocation concealment.
- Performance bias: blinding of participants and personnel (participants, treatment providers and outcome assessors).
- Detection bias: blinding of outcome assessment.
- Attrition bias: incomplete outcome data (i.e. incomplete follow-up outcomes and treatment-related complications).
- Reporting bias: selective reporting of outcomes.
- Other potential bias.

We will assess risk of bias in NRS according to the Cochrane 'Risk of Bias' in non-randomized Studies of Interventions (ROBINS-I) tool, and we will record results in the template ([Sterne 2016](#)). We will classify NRS as at 'high risk' of bias when they are at 'serious' risk according to the Cochrane ROBINS-I tool.

Two review authors (AS and CK) will apply the 'Risk of bias' tool independently and resolve differences by discussion or by appeal to a third review author (PL). We will judge each item as

being at high, low or unclear risk of bias as set out in the criteria displayed in [Appendix 3](#) ([Higgins 2011](#)). We will provide a quote from the study report or a statement (or both) as justification for the judgement for each item in the 'Risk of bias' table. We will summarise results in both a 'Risk of bias' graph and a 'Risk of bias' summary. When interpreting treatment effects and meta-analyses, we will take into account the risk of bias for the studies that contribute to that outcome. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the table.

Measures of treatment effect

For RCTs, we will use the following measures of the effect of treatment:

- For time-to-event outcome (overall and disease-free survival), we will use the hazard ratio (HR) with 95% confidence interval (CI).
- For dichotomous outcomes (adverse events and death, if it is not possible to use a hazard ratio) we will analyse data based on the number of events and the number of people assessed in the intervention and comparison groups. We will use these to calculate the RR and 95% CI.
- For continuous outcomes (severity of sexual dysfunction, cost-effectiveness and quality of life), we will analyse data based on the mean, standard deviation (SD) and number of people assessed for both the intervention and comparison groups to calculate the mean difference (MD) between treatment arms with a 95% CI. If the MD is reported without individual group data, we will use this to report the study results. If more than one study measures the same outcome using different tools, we will calculate the standardised mean difference (SMD) and 95% CI using the inverse variance method.

For NRS, we will use adjusted measures with their 95% CI for the primary effect measures when available. Odds ratio (OR) is an appropriate effect measure for both cohort and case-control studies and is commonly provided when adjusted analyses are obtained using logistic regression models. We will also use other effect measures if an appropriate adjusted OR is not available from the report. The effect measure may be an OR, RR or HR.

Unit of analysis issues

The units of analysis are the participants receiving any intervention. In a study with multiple intervention groups, we will combine all relevant experimental intervention groups into a single group to create a single pair-wise comparison ([Higgins 2011](#)).

Dealing with missing data

We will not impute missing outcome data for any of the outcomes. We will attempt to contact study authors to obtain missing data.

Assessment of heterogeneity

We will clinically assess heterogeneity by visual inspection of the forest plots. We will also assess statistical heterogeneity in each meta-analysis using the I^2 statistic and Chi^2 test (Deeks 2001; Higgins 2011). We will perform subgroup analysis to investigate the potential heterogeneity of the included studies. If there is evidence of substantial clinical and methodological heterogeneity across the included studies, we will not report pooled results from meta-analysis but will instead apply a narrative review approach to data synthesis.

Assessment of reporting biases

We will examine funnel plots corresponding to meta-analysis of the primary outcome to assess the potential for small study effects such as publication bias if more than 10 studies are identified. We plan to assess funnel plot asymmetry visually (Sterne 2011).

Data synthesis

We will carry out statistical analysis using the Cochrane Review Manager software (RevMan 2014), with the random-effects model for all meta-analyses (DeSimonian 1986).

- For time-to-event data, we will pool hazard ratios using the generic inverse variance method.
- For any dichotomous outcomes, we will calculate the risk ratio (RR) for each study and then pool these.
- For continuous outcomes, we will pool the mean differences (MD) between the treatment arms, if all trials measure the outcome on the same scale; otherwise we will pool standardised mean differences (SMD).
- We will pool any other treatment effects of the NRS, if appropriate, using the generic inverse variance method and report them on the natural (e.g. odds ratio) scale (Higgins 2011).

Main outcomes of 'Summary of findings' table for assessing the quality of the evidence

Appendix 4 displays a 'Summary of findings' table, which is prepared to summarise the results of the meta-analysis based on the methods described in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011). We will present the results of the meta-analysis for the outcomes as outlined in the [Types of outcome measures](#) section.

We will present the overall quality of the evidence for each outcome according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which takes into account issues not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity such as directness of results (Langendam 2013). We will create a 'Summary of findings' table based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and using GRADEpro GDT. We will

use the GRADE checklist and GRADE Working Group quality of evidence definitions (Meader 2014). We will downgrade the evidence from 'high' quality by one level for each serious (or by two for each very serious) limitation:

- **High quality:** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

We hypothesise that responses to intervention may differ according to stage of disease, histological subtypes and size of tumour. Therefore, we plan the following subgroup analyses if sufficient data are available:

- Stage of disease (IA2 versus IB1).
- Detailed histopathological type (squamous cell versus other histopathological types).
- Largest preoperative tumour size (< 2 versus ≥ 2 cm).

We will assess subgroup differences using the interaction tests available within Review Manager (RevMan 2014). We will report the results of subgroup analyses quoting the Chi^2 test and P value, the interaction test and the I^2 statistic value.

Sensitivity analysis

For all outcomes for which pooling is possible we will perform sensitivity analyses to assess the robustness of the findings by:

- repeating the analysis excluding unpublished studies (if any);
- repeating the analysis excluding NRS;
- repeating the analysis excluding RCTs judged to be at 'high' or 'unclear' risk of bias for allocation concealment.

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* Indicates the major publication for the study

APPENDICES

Appendix I. The International Federation of Gynecology and Obstetrics (FIGO) staging for carcinoma of the cervix

FIGO Stage			Description
I			The carcinoma is confined to the cervix
	IA		Invasive cancer identified only microscopically. (All gross lesions even with superficial invasion are Stage IB cancers.) Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm
		IA1	Measured invasion of stroma ≤ 3 mm in depth and ≤ 7 mm width
		IA2	Measured invasion of stroma > 3 mm and < 5 mm in depth and ≤ 7 mm width
	IB		Clinical lesions confined to the cervix, or preclinical lesions greater than stage IA
		IB1	Clinical lesions no greater than 4 cm in size
		IB2	Clinical lesions > 4 cm in size
II			The carcinoma extends beyond the uterus, but has not extended onto the pelvic wall or to the lower third of vagina
	IIA		Involvement of up to the upper 2/3 of the vagina. No obvious parametrial involvement
		IIA1	Clinically visible lesion ≤ 4 cm
		IIA2	Clinically visible lesion > 4 cm

(Continued)

	IIB	Parametrial involvement but not onto the pelvic sidewall
III		The carcinoma has extended onto the pelvic sidewall. On rectal examination, there is no cancer free space between the tumour and pelvic sidewall. The tumour involves the lower third of the vagina. All cases of hydronephrosis or non-functioning kidney should be included unless they are known to be due to other causes
	IIIA	Involvement of the lower vagina but no extension onto pelvic sidewall
	IIIB	Extension onto the pelvic sidewall, or hydronephrosis/non-functioning kidney
IV		The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum
	IVA	Spread to adjacent pelvic organs
	IVB	Spread to distant organs

Appendix 2. MEDLINE Ovid search strategy

1. Uterine Cervical Neoplasms/
 2. (cervi* adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*)).mp.
 3. 1 or 2
 4. exp Hysterectomy/
 5. hysterectom*.mp.
 6. ((uter* or womb) adj5 (remov* or excis*)).mp.
 7. 4 or 5 or 6
 8. exp Lymph Node Excision/
 9. (lymph* adj5 node* adj5 (excis* or dissect*)).mp.
 10. lymphadenectom*.mp.
 11. 8 or 9 or 10
 12. 3 and 7 and 11
- key:
- mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name

Appendix 3. 'Risk of bias' assessment

'Risk of bias' assessment based on Chapter 8 of [Higgins 2011](#):

- Random sequence generation
 - Low risk of bias, e.g. participants assigned to treatments on the basis of a computer-generated random sequence or a table of random numbers.
 - High risk of bias, e.g. participants assigned to treatments on the basis of date of birth, clinic ID number or surname, or no attempt to randomise participants.
 - Unclear risk of bias, e.g. not reported, information not available.
- Allocation concealment
 - Low risk of bias, e.g. where the allocation sequence could not be foretold.
 - High risk of bias, e.g. allocation sequence could be foretold by patients, investigators or treatment providers.
 - Unclear risk of bias, e.g. not reported.

- Blinding of participants and personnel
 - Low risk of bias if participants and personnel were adequately blinded.
 - High risk of bias if participants were not blinded to the intervention that the participant received.
 - Unclear risk of bias if this was not reported or unclear.
- Blinding of outcomes assessors
 - Low risk of bias if outcome assessors were adequately blinded.
 - High risk of bias if outcome assessors were not blinded to the intervention that the participant received.
 - Unclear risk of bias if this was not reported or is unclear.
- Incomplete outcome data: we will record the proportion of participants whose outcomes were not reported at the end of the study. We will code a satisfactory level of loss to follow-up for each outcome as:
 - Low risk of bias, e.g. if fewer than 20% of participants were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms.
 - High risk of bias, e.g. if more than 20% of participants were lost to follow-up or reasons for loss to follow-up differed between treatment arms.
 - Unclear risk of bias, e.g. if loss to follow-up was not reported.
- Selective reporting of outcomes
 - Low risk of bias, e.g. review reports all outcomes specified in the protocol.
 - High risk of bias, e.g. it is suspected that outcomes have been selectively reported in the study.
 - Unclear risk of bias, e.g. it is unclear whether outcomes have been selectively reported.
- Other bias
 - i) Low risk of bias, e.g. the review authors do not suspect any other source of bias and the trial appears to be methodologically sound.
 - ii) High risk of bias, e.g. the review authors suspect that the trial was prone to an additional bias.
 - iii) Unclear risk of bias, e.g. the review authors are uncertain whether an additional bias may have been present.

Appendix 4. Summary of findings table

Title: Simple versus radical hysterectomy in conjunction with pelvic lymphadenectomy for stage IA2-IB1 cervical cancer						
Patient or population: women with stage IA2-IB1 cervical cancer						
Settings: specialist hospital						
Intervention: simple hysterectomy with pelvic lymph node dissection						
Comparison: radical hysterectomy with pelvic lymph node dissection						
Outcomes	Illustrative comparative risks*		Relative effect (95% CI)	No of participants (studies)	Quality of evidence (GRADE)	Comment
	Assumed risk	Corresponding risk				
Overall survival						
Progression-free survival						
Adverse events						
Sexual dysfunction						

(Continued)

Cost-effectiveness						
Quality of life						
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; HR: hazard ratio; MD: mean difference; RR: risk ratio; OR: odds ratio						
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.						

CONTRIBUTIONS OF AUTHORS

Amornrat Supoken: conceived the review question, developed, co-ordinated and completed the protocol.

Chumnan Kietpeerakool: conceived the review question, developed and completed the protocol.

Malinee Laopaiboon: performed part of the editing of the protocol and advised on part of the protocol.

Pisake Lumbiganon: developed and co-ordinated the development of the protocol, edited the protocol and advised on the protocol.

DECLARATIONS OF INTEREST

Amornrat Supoken: nothing to declare.

Chumnan Kietpeerakool: nothing to declare.

Malinee Laopaiboon: nothing to declare.

Pisake Lumbiganon: nothing to declare.

SOURCES OF SUPPORT

Internal sources

- Department of Obstetrics and Gynaecology, Faculty of Medicine, Khon Kaen University, Thailand.
- Department of Biostatistics and Demography, Faculty of Public Health, Khon Kaen University, Thailand.
- Cochrane Thailand, Thailand.

External sources

- Thailand Research Fund (Distinguished Professor Award), Thailand.



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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
BACKGROUND	1
OBJECTIVES	2
METHODS	2
ACKNOWLEDGEMENTS	5
REFERENCES	5
APPENDICES	7
CONTRIBUTIONS OF AUTHORS	8
DECLARATIONS OF INTEREST	8
SOURCES OF SUPPORT	9

Antibiotics for the prevention of infection after continence surgery in women with stress urinary incontinence

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To determine the effectiveness and adverse effects of prophylactic antibiotics for preventing infections after continence surgery in women with stress urinary incontinence.

BACKGROUND

Description of the condition

Stress urinary incontinence (SUI) is defined as involuntary leakage of urine when increasing intra-abdominal pressure suddenly, as occurs during coughing, sneezing, and laughing (Abrams 2003). This symptom leads to physical, psychological, sexual, and social problems (Coyne 2012; Akkus 2015). There are two types of surgical correction for SUI: traditional techniques, and minimally-invasive procedures such as mid-urethral slings and injectable urethral bulking agents (Davis 2013; NICE 2013). Traditional continence surgery includes open retropubic colposuspension, laparoscopic colposuspension, bladder neck needle suspension, sub-urethral sling, and anterior vaginal wall repair. Recently, continence

surgery has made a major advance with the introduction of mid-urethral slings, a minimally-invasive technique (Garely 2014; Ford 2015). A mid-urethral sling is a surgical procedure that aims to place a synthetic polypropylene support tape under the mid part of the urethra, to prevent it from dropping during physical activity. The placement of support restores the normal anatomy of the urinary bladder and urethra, thus preventing or minimising urine leakage. Another minimally-invasive treatment for SUI is an injection of biomaterial bulking agent into the urethral wall around the bladder neck to improve urethral coaptation. This treatment is frequently reserved as an option for patients unwilling or medically unfit to undergo surgery (Zoorob 2012; Davis 2013). Infections are always a risk with any surgical procedure and represent a significant source of patient morbidity and potential mortality, and cost to health services (ACOG 2009; Van Eyk 2012).

Continence surgery for SUI is no exception. Previous studies reported that the infection following colposuspension, a traditional surgical technique for SUI, was 21% and the most common complications included wound infection (5.5% to 17.1%) and urinary tract infection (UTI) (3.9% to 10%) (Mainprize 1988; Chai 2009). The most common infections following mid-urethral sling surgery is postoperative UTI which ranges from 2.6% to 20.7% depending on the diagnostic method and criteria applied, time period of observation, and time of an indwelling urinary catheter (Swartz 2010; Dieter 2012; Harmanli 2012). Women undergoing mid-urethral sling surgery who require postoperative catheterisation are at an increased risk of UTI (odds ratio (OR) 6.6, 95% confidence interval (CI) 1.8 to 24.5) (Dieter 2012). Wound infections following mid-urethral sling surgery are generally less than 1% (Swartz 2010; Harmanli 2012).

Description of the intervention

Prophylactic antibiotics may be given during surgery in an attempt to minimise the risk of postoperative bacterial infections. The fundamental purpose of prophylactic antibiotics is to reduce the colonisation of potential micro-organisms introduced at the time of an operation. An adequate bactericidal concentration of prophylactic antibiotic in blood and tissue can enhance the natural host immune defence mechanism and help to kill bacteria (ACOG 2009; Van Eyk 2012). The appropriate type of prophylactic antibiotic for each surgical procedure mainly depends on the type of bacteria exposed during an operation. The appropriate time for initiating prophylactic antibiotics is shortly before or at the time of bacterial inoculation. In general, a single dose of prophylactic antibiotics is quite effective. Additional doses are indicated for patients who undergo a lengthy operation and/or experience significant blood loss. Because of an increased risk of infectious complication in obese patients, the dose of prophylactic antibiotics given to these patients should be increased to achieve therapeutic levels of antibiotic agents in subcutaneous adipose tissue (ACOG 2009; Pevzner 2011; Van Eyk 2012).

How the intervention might work

The perioperative delivery of antibiotics has been reported to be an effective intervention for reducing the risk of healthcare-acquired infections in a variety of surgical settings (Tanos 1994; Schiøtz 2002; Köckerling 2015). Among women undergoing transabdominal hysterectomy, antibiotics for infection prevention reduced the risk of infection by approximately 65% (OR 0.35, 95% CI 0.3 to 0.4) (Tanos 1994). The use of antibiotics markedly reduced the incidence of postoperative bacteriuria and urinary tract infection among women undergoing vaginal reconstructive surgery compared to the placebo group (6.7% versus 20.0%, respectively) (Schiøtz 2002). In addition, prophylactic antibiotics decreased the

rates of postoperative impaired wound healing (OR 0.68, 95% CI, 0.48 to 0.96), and deep infections with mesh involvement (OR 0.52, 95% CI 0.34 to 0.80) among patients undergoing open inguinal hernia surgical repair (Köckerling 2015). Based on these provocative findings, there is a theoretical possibility that prophylactic antibiotics may effectively decrease the risk of infection following continence surgery for women with SUI.

Why it is important to do this review

Postoperative infections prolong recovery time and increase healthcare costs (ACOG 2009; Van Eyk 2012). Effective interventions for preventing this complication are fundamentally important. Although prophylactic antibiotics seem to be the most promising intervention, to date there has been no systematic review evaluating their effectiveness for preventing infection after continence surgery. We will therefore conduct a Cochrane systematic review to evaluate the effectiveness and adverse effects of prophylactic antibiotics for preventing infection among women with SUI undergoing continence surgery.

OBJECTIVES

To determine the effectiveness and adverse effects of prophylactic antibiotics for preventing infections after continence surgery in women with stress urinary incontinence.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) or quasi-RCTs regardless of blinding, language, publication and sample size.

Types of participants

We will include studies of adult women aged 18 years and over undergoing any type of surgery for stress urinary incontinence (SUI).

We will exclude studies of women who had continence surgery with additional surgery; a history of febrile illness or antibiotic use within three days preoperatively; risk factors for endocarditis such as patients with mechanical heart valve or rheumatic heart disease; current pregnancy; or who were immunocompromised hosts such as patients with immunosuppressive agents or chemotherapy, autoimmune diseases or HIV infection except diabetes mellitus.

Types of interventions

- Prophylactic antibiotics (single drug or combined drugs) versus placebo or no treatment
- One type or class of prophylactic antibiotics (single drug or combined drugs) versus another type or class
- One dose of prophylactic antibiotics (single drug or combined drugs) versus another dose (e.g. higher versus lower dose)
- One route of administration of a prophylactic antibiotic (single drug or combined drugs) versus another (e.g. intravenous, intravesical, or oral administration)
- One duration of administration of a prophylactic antibiotic (single drug or combined drugs) versus another duration (e.g. shorter versus longer duration)

Types of outcome measures

Primary outcomes

1. Surgical site infections (SSIs): persistent discharge from incision, induration with pain, subcutaneous fluid collection, or incisional wound break down
2. Adverse effects of antibiotics such as allergic reaction, diarrhoea, and bacterial resistance as defined by the study

Secondary outcomes

1. Symptomatic UTI: a urine culture showed growth of at least 100,000 colony-forming units of a urinary tract pathogen per mL with symptoms)
2. Febrile morbidity: two oral temperature measurements of 100.4°F/37.8 degree Celsius and greater occurring at least 6 hours apart, excluding the first 24 hours after surgery
3. Sepsis or bacteraemia
4. Mesh exposure: visible mesh in the vagina after the surgery, or infected mesh
5. Readmission to hospital because of infection
6. Length of hospital stay for surgery (days)
7. Others

Quality of evidence

The review authors will classify primary and secondary outcomes, as defined above, as 'critical,' 'important' or 'not important' for decision making from the participant's perspective. According to the GRADE working group recommendation, the review authors will include the following outcomes for assessing the quality of evidence using GRADE methodology.

1. Surgical site infections.
2. Adverse effects of antibiotics such as allergic reaction, diarrhoea, and bacterial resistance.

3. Symptomatic UTI.
4. Febrile morbidity.
5. Sepsis or bacteraemia.
6. Mesh exposure.

We will use the GRADE checklist and GRADE Working Group quality of evidence definitions (Meader 2014), as follows. .

- High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low quality: confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

We will downgrade the evidence from 'high' quality by one level for serious limitations (or by two levels for very serious limitations).

Search methods for identification of studies

In consultation with the Cochrane Information Specialist, we will search for studies that meet the inclusion criteria.

Electronic searches

This review will draw on the search strategy developed for the Cochrane Incontinence Group. We will identify relevant trials from the Cochrane Incontinence Group Specialised Trials Register. For more details of the search methods used to build the Specialised Register please see the Group's [module](#) in the *Cochrane Library*. The register contains trials identified from the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, MEDLINE In-Process, MEDLINE Epub Ahead of Print, CINAHL, [ClinicalTrials.gov](#), [WHO ICTRP](#), [UK Clinical Research Network Portfolio](#) and handsearching of journals and conference proceedings. Many of the trials in the Cochrane Incontinence Group Specialised Register are also contained in CENTRAL. The terms that will be used to search the Incontinence Group Specialised Register are given in [Appendix 1](#). We will also search LILACS (1982 to present).

Searching other resources

We will search the following databases for grey literature: Open-Grey (www.opengrey.eu/) and Index to theses ([ProQuest Dissertations & Theses: UK & Ireland](#)). We will also handsearch reference lists of relevant articles retrieved by the search, and contact trial authors to obtain additional data if necessary.

Data collection and analysis

Selection of studies

We will export all titles and abstracts retrieved by electronic searching to EndNote (endnote.com/). After duplicates have been removed, we will transfer these data to Covidence (www.covidence.org) We will exclude those studies which clearly do not meet the inclusion criteria. We will obtain copies of the full-text of potentially relevant references. Two review authors (TT and PB) will independently assess the eligibility of the retrieved reports/publications. We will resolve any disagreement through discussion or, if required, we will consult a third person (CC or PL). We will identify and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will use the details regarding the selection process in Covidence to complete a PRISMA flow diagram ([Liberati 2009](#)) and 'Characteristics of excluded studies' table.

Data extraction and management

Two review authors (TT and PB) will independently extract study characteristics and outcome data from included studies using Covidence. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third person (PL). One review author (TT) will transfer data into Review Manager 5 ([RevMan 2014](#)). A second review author (CK) will check study characteristics for accuracy against the trial report. Where feasible, we will extract data based on an intention-to-treat analysis, in which participants were analysed in the groups to which they were initially randomised.

Assessment of risk of bias in included studies

We will assess and report on the methodological risk of bias of included studies in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)), which recommends the explicit reporting of the following individual elements:

1. Selection bias: random sequence generation and allocation concealment
2. Performance bias: blinding of participants and personnel (patients and treatment providers)
3. Detection bias: blinding of outcome assessment
4. Attrition bias: incomplete outcome data
5. Reporting bias: selective reporting of outcomes

Two review authors (TT and PB) will apply the 'Risk of bias' tool independently and differences will be resolved by discussion or by appeal to a third review author (PL). We will judge each item as being at high, low or unclear risk of bias as displayed in [Appendix 2](#), based on *Cochrane Handbook* suggestions ([Higgins 2011](#)). We will provide a quote from the study report and/or a statement as

justification for the judgement for each item in the 'Risk of bias' table. We will summarise results in both a 'Risk of bias' graph and a 'Risk of bias' summary. When interpreting treatment effects and meta-analyses, we will take into account the risk of bias for the studies that contribute to that outcome. Where information on risk of bias relates to unpublished data or correspondence with trial authors, we will note this in the table.

Measures of treatment effect

For dichotomous outcomes, such as incidence of infections after operation and incidence of adverse events, we will use the risk ratio (RR) and its 95% confidence interval (CI). For continuous outcomes, such as length of hospital stay, we will use the mean difference (MD) if outcomes are measured in the same way between trials. We will use the standardised mean difference (SMD) if more than one trial measure the same outcome using different tools.

Unit of analysis issues

The unit of analysis of RCTs and quasi-RCTs is individual participants. When including non-standard designs, issues with the unit of analysis can occur. We could adopt the following approaches if appropriate ([Higgins 2011](#)):

- multiple treatment arms: we will split the control group into two or more groups with a smaller sample size if the data would be combined in the same meta-analysis as suggested in the *Cochrane Handbook for Systematic Review of Interventions* ([Higgins 2011](#));
- repeated measures: we will report different outcomes per period ([Higgins 2011](#)).

Dealing with missing data

We will not impute missing outcome data for the primary outcome and we will attempt to contact study authors to obtain missing data. If data are missing to the extent that we cannot include the study in the analysis, we will present the results in a narrative way.

Assessment of heterogeneity

Heterogeneity will be clinically assessed by visual inspection of the forest plots. We will also assess statistical heterogeneity in each meta-analysis using the I^2 statistic and χ^2 test. We will regard heterogeneity as substantial if the I^2 statistic value is greater than 50%, or there is a low P value (< 0.10) in the χ^2 test for heterogeneity ([Deeks 2001](#); [Higgins 2003](#)). If there is substantial statistical heterogeneity, we will carry out subgroup analyses to assess differences between the included studies. However, if there is clinical, methodological or remarkably high statistical heterogeneity (I^2 greater than 80%) across included studies, we will not report pooled results from meta-analysis but will instead use a narrative approach to data synthesis.

Assessment of reporting biases

We will examine funnel plots corresponding to meta-analysis of the primary outcome to assess the potential for small study effects such as publication bias if more than ten studies are identified. If asymmetry is suggested by a visual assessment, we will perform sensitivity analysis to investigate whether it affects the pooled results (Sterne 2011).

Data synthesis

If sufficient clinically-similar studies (in terms of study participants, settings, intervention, comparison and outcome measures) are available to ensure meaningful conclusions, and if statistical heterogeneity is low, we will pool the studies' results in meta-analyses using a fixed-effect model in Review Manager software (RevMan 2014). If there is no variability between the included studies (clinical heterogeneity) but statistical heterogeneity is substantial, we will use a random-effects model with inverse variance for meta-analysis (DerSimonian 1986).

For dichotomous outcomes, we will calculate the RR for each study and these will then be pooled.

For continuous outcomes, we will pool the MD between the treatment arms, if all trials measure the outcome on the same scale; otherwise we will pool SMD.

We will prepare a 'Summary of findings' table to present the results of meta-analysis, as per the method described in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of interventions* (Schünemann 2011). We will use the GRADEpro GDT 2015 software to do so.

Subgroup analysis and investigation of heterogeneity

Where data are available, we will conduct subgroup analyses to determine the impact of the following factors on the magnitude of the effect:

- obese women versus non-obese women (women with body mass index (BMI) ≥ 30 versus those with lower BMI);
- women with diabetes versus women without diabetes;
- poor voiding (slow stream, large residuals) versus normal voiding at cystometry before surgery;
- type of surgery (traditional techniques versus minimally invasive mid-urethral sling); and
- short- versus long-term use of an antimicrobial (single or combined). A subgroup analysis will include patients who received only a single preoperative dose versus those who received at least a second intraoperative dose of antibiotic, or postoperative dosing, or both.

Sensitivity analysis

We will perform a sensitivity analysis to assess the robustness of the findings by:

- repeating the analysis excluding unpublished studies (if any);
- repeating the analysis excluding quasi-RCTs (if any); and
- repeating the analysis for only RCTs but excluding studies judged to be at 'high' or 'unclear' risk of bias for allocation concealment.

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* Indicates the major publication for the study

APPENDICES

Appendix 1. Search strategy: Cochrane Incontinence Group Specialised Register

The terms that will be used to search the Incontinence Group Specialised Register are:

((({DESIGN.CCT*} OR {DESIGN.RCT*})) AND {INTVENT.SURG*} AND {TOPIC.URINE.INCON*} AND ({INTVENT.PREVENT*} OR {INTVENT.CHEM*}))

As Cochrane now undertakes a centralised search of Embase for randomised and quasi-randomised controlled trials which are incorporated into CENTRAL, and as CENTRAL is searched for the Specialised Register, there will be no separate search of Embase for this review.

(All searches will be of the keyword field of [Reference Manager 2012](#)).

Appendix 2. 'Risk of bias' assessment

Our assessment of risk of bias will be based on chapter 8 of [Higgins 2011](#) as follows:

Random sequence generation

- i) Low risk of bias e.g. participants assigned to treatments on the basis of a computer-generated random sequence or a table of random numbers
- ii) High risk of bias e.g. participants assigned to treatments on the basis of date of birth, clinic identification number or surname, or no attempt to randomise participants
- iii) Unclear risk of bias e.g. not reported, information not available

Allocation concealment

- i) Low risk of bias e.g. where the allocation sequence could not be foretold
- ii) High risk of bias e.g. allocation sequence could be foretold by patients, investigators or treatment providers
- iii) Unclear risk of bias e.g. not reported

Blinding of participants and personnel

- i) Low risk of bias if participants and personnel were adequately blinded
- ii) High risk of bias if participants were not blinded to the intervention that the participant received
- iii) Unclear risk of bias if this was not reported or unclear

Blinding of outcomes assessors

- i) Low risk of bias if outcome assessors were adequately blinded
- ii) High risk of bias if outcome assessors were not blinded to the intervention that the participant received
- iii) Unclear risk of bias if this was not reported or is unclear

Incomplete outcome data

We will record the proportion of participants whose outcomes were not reported at the end of the study. We will code a satisfactory level of loss to follow-up for each outcome as:

- i) Low risk of bias e.g. if fewer than 20% of participants were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms
- ii) High risk of bias e.g. if more than 20% of participants were lost to follow-up or reasons for loss to follow-up differed between treatment arms
- iii) Unclear risk of bias e.g. if loss to follow-up was not reported

Selective reporting of outcomes

- i) Low risk of bias e.g. the study reports all outcomes specified in the protocol
- ii) High risk of bias e.g. the study is suspected of having outcomes that have been selectively reported
- iii) Unclear risk of bias if this was unclear

CONTRIBUTIONS OF AUTHORS

Teerayut Temtanakitpaisan (TT) conceived the review question, developed, is the main person responsible for writing the protocol.

Pranom Buppasiri (PB) developed and advised on part of the protocol.

Chompilas Chongsomchai (CC) performed part of the editing of the protocol and advised on part of the protocol.

Chumnan Kietpeerakool (CK) developed, coordinated, and critically edited the protocol.

Pisake Lumbiganon (PL) developed and coordinated the development of the protocol, and critically edited the protocol.

Malinee Laopaiboon (ML) performed part of the editing of the protocol and advised on part of the protocol.

All authors approved the final version of the protocol prior to submission.

DECLARATIONS OF INTEREST

TT: none known

PB: none known

CC: none known

CK: none known

PL: none known

ML: none known

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Luvira V, Satitkarnmanee E, Pugkhem A, Kietpeerakool C, Lumbiganon P, Kamsa-ard S, Pattanittum P.

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
BACKGROUND	1
OBJECTIVES	3
METHODS	3
ACKNOWLEDGEMENTS	7
REFERENCES	8
APPENDICES	11
CONTRIBUTIONS OF AUTHORS	14
DECLARATIONS OF INTEREST	14
SOURCES OF SUPPORT	15

Postoperative adjuvant chemotherapy for resectable cholangiocarcinoma

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the benefits and harms of adjuvant chemotherapy for people with cholangiocarcinoma who have undergone curative-intent resection.

BACKGROUND

Description of the condition

Cholangiocarcinoma is a malignant epithelial tumour arising in the bile duct (intrahepatic and extrahepatic bile duct). Several conditions have been established as risk factors associated with cholangiocarcinoma including cirrhosis, hepatitis B, hepatitis C, chronic inflammation with liver injury secondary to the primary sclerosing cholangitis, and infection with *Opisthorchis viverrini* (*O. viverrini*) (South Asian liver fluke) and *Clonorchis sinensis* (*C. sinensis*) (Chinese liver fluke). The age-standardised incidence rates of cholangiocarcinoma vary widely between the different geographical regions, largely due to variations in regional environmental

risk factors. Cholangiocarcinoma is relatively rare among Western countries with an age-standardised incidence rate between 0.3 and 2 per 100,000 person-years. The age-standardised incidence rate of cholangiocarcinoma in Asian countries ranges from 1 to 85 per 100,000 person-years. The highest age-standardised incidence rate of cholangiocarcinoma is found in the northeast provinces of Thailand where the liver fluke *O. viverrini* is endemic (up to 113 per 100,000 person-years in men and 50 per 100,000 person-years in women) (Parkin 2002; Sripa 2008; Bergquist 2015; Khuntikeo 2016).

Cholangiocarcinoma is commonly classified based on anatomical location. The intrahepatic type is defined as a cholangiocarcinoma that arises in a bile duct proximal to a second-degree bile duct. Perihilar type is located in the bile duct between a second-degree bile duct and a junction of cystic duct and a common bile duct. Distal

type is localised in the area between the insertion of a cystic duct and the ampulla of Vater (Nakeeb 1996). Appendix 1 displays the American Joint Committee staging for Cancer (AJCC) tumour-nodes metastasis (TNM) staging system for cholangiocarcinoma (NCCN 2016).

Complete resection remains the gold standard of treatment for cholangiocarcinoma. Malignancy positive surgical margins and regional lymph node metastasis negatively impact on the survival of people with cholangiocarcinoma who undergo curative intent resection (Isa 2001; Weber 2001; Pattanathien 2013; Titapun 2015). Median survivals of people who have negative resection margins range from 25 to 61 months compared to 12 to 20 months in people with positive resection margins (Isa 2001; Pattanathien 2013; Titapun 2015). Median survivals are 10 to 12 months in people with negative resection margins and 27 to 63 months in people with positive resection margins, for people who have a lymph node metastasis and those without a lymph node metastasis (Isa 2001; Pattanathien 2013; Titapun 2015).

Description of the intervention

Chemotherapy is the use of drugs to treat cancer, principally by inhibiting the growth and division of cancer cells and promoting cell death. Adjuvant (supplementary treatment after initial treatment) chemotherapy can be defined as an additional chemotherapy given immediately after primary surgery or primary radiotherapy in an attempt to lessen the risk of the cancer returning by eradicating residual diseases, particularly micrometastatic lesions that are supposed to be outside the field of the primary treatment covered (Carter 1986; Powell 1987). Chemotherapy agents can be administered locally (e.g. topical application or intracavitary injection) or systemically (e.g. oral, intramuscular injection, or intravenous injection) administered. The choice of chemotherapy agents for each patient mainly depends on the type and stage of cancer, patient's performance status, and details of previous treatment received (Carter 1986; Powell 1987). Although the best chemotherapy for cholangiocarcinoma remains to be determined, 5-fluorouracil and gemcitabine, as a single chemotherapeutic agent or in combination with other drugs, have been proposed as active and well-tolerated regimens (Thongprasert 2005).

How the intervention might work

The mainstay of treatment of cholangiocarcinoma is surgical resection (Razumilava 2014; Luvira 2016). The operation for intrahepatic cholangiocarcinoma is resection of the involved hemiliver. For perihilar cholangiocarcinoma, additional bile duct resection, complete caudate lobe resection, and hepato-duodenal lymph node dissection are required. Pancreaticoduodenectomy is the operation of choice for people with distal cholangiocarcinoma (Razumilava 2014). Although complete resection offers the best

chance of cure for people with cholangiocarcinoma, recurrence can be high, ranging from 46% to 61% (Weber 2001; Yamamoto 2001; Hyder 2013). Cholangiocarcinoma can recur locally in the remaining liver or systemically in the distant organs. It is generally accepted that the recurrence of cancers arises not only because of inadequacy of surgical resection, but it is also secondary to pre-existing microscopic tumour that spread systematically (Al Ustwani 2012). This concept motivates the attempt of postoperative adjuvant chemotherapy to supplement surgical resection in order to eradicate microscopic disease following resection of clinically detectable lesions of cholangiocarcinoma. Adjuvant chemotherapy given after surgical resection may reduce the risk of the cancer recurrence by eradicating residual diseases and micrometastatic lesions.

A number of Cochrane systematic reviews have addressed the benefits of adjuvant chemotherapy given after primary surgery in lengthening survival in a variety of cancers (Figueredo 2008; Petersen 2012; Burdett 2015; Lawrie 2015). In people with completely resected stage II colon cancer, adjuvant chemotherapy reduced the risk of cancer recurrence by approximately 17% compared with the control group who underwent surgery alone (risk ratio (RR) for disease-free survival 0.83, 95% confidence interval (CI) 0.75 to 0.92; Figueredo 2008). In people with rectal cancer undergoing curative intent surgery, adjuvant chemotherapy reduced the risk of death by 17% (hazard ratio (HR) 0.83, 95% CI 0.76 to 0.91) and disease recurrence by 25% (HR 0.75, 95% CI 0.68 to 0.83) among people undergoing postoperative adjuvant chemotherapy compared with people undergoing observation (Petersen 2012). When compared with the control group, adjuvant postoperative chemotherapy given to women with early-stage ovarian cancer reduced the 10-year risk of death (RR 0.76, 95% CI 0.62 to 0.94), as did the risk of disease progression (RR 0.72, 95% CI 0.60 to 0.87; Lawrie 2015). Additionally, compared to surgery alone, adjuvant chemotherapy in people with resected early-stage non-small cell lung cancer reduced the risk of death by approximately 14% (HR 0.86, 95% CI 0.81 to 0.92; Burdett 2015).

Why it is important to do this review

Although various novel surgical techniques for treating cholangiocarcinoma have been developed, prognosis of patients after resection remains poor. Therefore, interventions for improving treatment outcomes among people with cholangiocarcinoma operated for cure are needed. The high tendency for cholangiocarcinomas to recur provides a rationale for adjuvant therapy after definitive surgery (Yang 2014). Postoperative adjuvant chemotherapy appears to be a promising adjuvant treatment for people with cholangiocarcinoma. However, to our knowledge, there has been no systematic review evaluating the effectiveness of adjuvant chemotherapy following surgical resection of cholangiocarcinoma. Therefore, we will conduct a Cochrane systematic review to evaluate the

effectiveness and safety of adjuvant chemotherapy for people with cholangiocarcinoma undergoing curative-intent surgery.

with control group (receiving no treatment, placebo, or different regimen of chemotherapy).

OBJECTIVES

To assess the benefits and harms of adjuvant chemotherapy for people with cholangiocarcinoma who have undergone curative-intent resection.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised clinical trials irrespective of blinding, publication status, or language. We will exclude quasi-randomised and observational studies from the analysis on benefits, but we will include non-randomised studies identified with the search for RCTs for the assessment of adverse events. By focusing mainly on randomised clinical trials, we are aware that the review may be biased towards assessments of benefits. We will include unpublished trials only if trial data and methodological descriptions were provided in written form or obtained through direct contact with study authors.

Types of participants

Adults (aged 18 years or older) of both sexes who underwent curative-intent resection for cholangiocarcinoma and received any type of postoperative adjuvant chemotherapy compared with people with the same condition but receiving no postoperative treatment, or receiving a different regimen of adjuvant chemotherapy. We will include only trials with participants whose diagnosis of cholangiocarcinoma was established by pathological examination of surgical specimens. According to the definition of cholangiocarcinoma, we will not include participants with cancer of gallbladder and ampulla of Vater. We will also include people receiving any type of neoadjuvant treatment prior to operation, who were subsequently randomised to postoperative adjuvant chemotherapy, if the cointerventions were equally applied in the trial groups.

Types of interventions

All regimens of postoperative chemotherapy (intravenous infusion, intravenous bolus, intraportal infusion, and oral administration of single or combination chemotherapy regimens) compared

Types of outcome measures

Primary outcomes

- All-cause mortality (death from any cause).
- Serious adverse events. We will use the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice's definition of a serious adverse event (ICH-GCP 1997), that is, any untoward medical occurrence that results in death, is life threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. We will consider all other adverse events as non-serious (see below).
- Health-related quality of life (as reported by the participants and as assessed by standard grading systems measured on a valid scale (e.g. Functional Assessment of Cancer Therapy-Hepatobiliary cancers (FACT-Hep 2015)).

Secondary outcomes

- Cancer-related mortality (death from cancer).
- Time to recurrence of the tumour.
- Non-serious adverse events.

Search methods for identification of studies

Electronic searches

We will search The Cochrane Hepato-Biliary Group Controlled Trials Register (Gluud 2017), the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (latest issue), MEDLINE Ovid (1946 to present), Embase Ovid (1974 to present), LILACS (1982 to present; Bireme), and Science Citation Index Expanded (1900 to present; Web of Science) (Royle 2003). Appendix 2 provides the preliminary search strategies for identification of relevant studies for our review.

We will endeavour to identify randomised clinical trials referenced in non-English databases, using our personal contacts or local access, or asking the Cochrane Hepato-Biliary Group Information Specialist, Sarah Klingenberg, to contact Cochrane collaborators from around the world, with the same intent.

We will not restrict our searches by language.

Searching other resources

We will handsearch reference lists of articles retrieved by the search and contact trial authors to obtain additional data if necessary.

We will search online trial registries such as ClinicalTrials.gov (www.clinicaltrials.gov/), European Medicines Agency (EMA) (www.ema.europa.eu/ema/), World Health Organization (WHO) International Clinical Trial Registry Platform (www.who.int/ictip/), Google Scholar (scholar.google.com), the Food and Drug Administration (FDA) (www.fda.gov), and pharmaceutical company sources for ongoing or unpublished trials.

We will contact the Cholangiocarcinoma Foundation (cholangiocarcinoma.org), the Alan Morement Memorial Fund (ammf.org.uk), and the Cholangiocarcinoma Foundation of Thailand (cloud.cascap.in.th) to ask for additional relevant data.

Data collection and analysis

We will perform the review following the recommendations of Cochrane (Higgins 2011) and the Cochrane Hepato-Biliary Group Module (Gluud 2017). We will perform the analyses using Review Manager 5 (RevMan 2014) and Trial Sequential Analysis (Thorlund 2011; TSA 2011; Wetterslev 2017).

Selection of studies

We will download all titles and abstracts retrieved by electronic searching to a reference management database (Endnote). After duplicates are removed, we will transfer these data to Covidence (www.covidence.org). After excluding studies that clearly do not match the review criteria, we will obtain the full text of potentially relevant references for detailed reviewing. Two review authors (VL and ES) will independently assess the eligibility of the retrieved publications. We will resolve any disagreement through discussion or, if necessary, we will consult a third review author (AP or CK). We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will use the details of the selection process in Covidence to create a PRISMA flow diagram (Liberati 2009).

Data extraction and management

Two review authors (VL and ES) will independently extract study characteristics and outcome data from included studies using Covidence. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third review author (AP or CK). One review author (PP) will transfer data into Review Manager 5 (RevMan 2014). A second review author (PL) will check study characteristics for accuracy against the trial report. For included studies, we will extract the following data: author, year of publication, and journal citation (including language);

country; setting; inclusion and exclusion criteria; study methodology; study population and characteristics; total number enrolled, participant characteristics, age, comorbidities, other baseline characteristics, stage of cholangiocarcinoma, tumour size in largest diameter, histopathological type, status of surgical margin and lymph nodes, volume of residual lesion; intervention details, regimens of adjuvant chemotherapy, dose of adjuvant chemotherapy; comparison details; risks of bias in study (see below); duration of follow-up; outcomes; results; funding for trial, notable conflicts of interest of trial authors.

We plan the following.

- For time to event data (e.g. all-cause mortality and cancer-related mortality), we will extract the log of the hazard ratio (log(HR)) and its standard error from trial reports. If these are not reported, we will attempt to estimate the log (HR) and its standard error using the methods of Parmar 1998.
- For dichotomous outcomes (e.g. adverse events), we will extract the number of people in each treatment arm who experienced the outcome of interest and the number of people assessed at end of follow-up, to estimate an RR.
- For continuous outcomes (e.g. health-related quality of life measures), we will extract the final value and standard deviation of the outcome of interest and the number of people assessed at end of follow-up in each treatment arm, to estimate the mean difference between the treatment arms.

We will calculate 95% CIs for each estimate.

Where possible, all data extracted will be those relevant to an intention-to-treat analysis, in which participants will be analysed in groups to which they were assigned.

Assessment of risk of bias in included studies

Two review authors (VL and ES) will independently assess the risk of bias of each included trial according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), the Cochrane Hepato-Biliary Group Module (Gluud 2017), and methodological studies (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Savović 2012a; Savović 2012b; Lundh 2017). We will use the following definitions in the assessment of risk of bias.

Allocation sequence generation

- Low risk of bias: the study performed sequence generation using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if an independent person not otherwise involved in the study performed them.
- Unclear risk of bias: the study authors did not specify the method of sequence generation.

- High risk of bias: the sequence generation method was not random. We will only include such studies for assessment of harms.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. A central and independent randomisation unit controlled allocation. The investigators were unaware of the allocation sequence (e.g. if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Unclear risk of bias: the study authors did not describe the method used to conceal the allocation so the intervention allocations may have been foreseen before, or during, enrolment.
- High risk of bias: it is likely that the investigators who assigned the participants knew the allocation sequence. We will only include such studies for assessment of harms.

Blinding of participants and personnel

- Low risk of bias: any of the following: no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; or blinding of participants and key study personnel ensured, and it is unlikely that the blinding could have been broken.
- Unclear risk of bias: any of the following: insufficient information to permit judgement of 'low risk' or 'high risk;' or the trial did not address this outcome.
- High risk of bias: any of the following: no blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; or blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.

Blinded outcome assessment

- Low risk of bias: any of the following: no blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; or blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
- Unclear risk of bias: any of the following: insufficient information to permit judgement of 'low risk' or 'high risk;' or the trial did not address this outcome.
- High risk of bias: any of the following: no blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; or blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. The study used sufficient methods, such as multiple imputation, to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: the trial reported the following predefined outcomes: all-cause mortality, serious adverse events, and time to recurrence of the tumour. If the original trial protocol is available, the outcomes should be those called for in that protocol. If the trial protocol was obtained from a trial registry (e.g. www.clinicaltrials.gov), the outcomes sought should be those enumerated in the original protocol if the trial protocol was registered before or at the time that the trial was begun. If the trial protocol was registered after the trial was begun, we will not consider those outcomes to be reliable.
- Unclear risk of bias: the study authors do not report all predefined outcomes fully, or it is unclear whether the study authors recorded data on these outcomes or not.
- High risk of bias: the study authors do not report one or more predefined outcomes.

For-profit bias

- Low risk of bias: the trial appears free of industry sponsorship or other type of for-profit support that could manipulate the trial design, conductance, or trial results.
- Unclear risk of bias: the trial may or may not be free of for-profit bias as the trial does not provide any information on clinical trial support or sponsorship.
- High risk of bias: the trial is sponsored by industry or received other type of for-profit support.

Other bias

- Low risk of bias: the trial appears to be free of other factors that could put it at risk of bias.
- Unclear risk of bias: the trial may or may not be free of other factors that could put it at risk of bias.
- High risk of bias: there were other factors in the trial that could put it at risk of bias.

We will judge trials to be at a low risk of bias if they are assessed as having a low risk of bias in all the above domains. We will judge trials to be at a high risk of bias if they are assessed as having an

unclear risk of bias or a high risk of bias in one or more of the above domains.

We will resolve any differences in opinion through discussion, and in the case of unsettled disagreements, a third review author will adjudicate.

Measures of treatment effect

We will use the following measures of the effect of treatment.

- For mortality, we will use the HR and 95% CI.
- For dichotomous outcomes, we will analyse data based on the number of events and the number of people assessed in the intervention and comparison groups. We will use these to calculate the RR and 95% CI and Trial Sequential Analysis-adjusted CI.
- For continuous outcomes, we will analyse data based on the mean, standard deviation, and number of people assessed for both the intervention and comparison groups to calculate the mean difference between treatment arms with a 95% CI and Trial Sequential Analysis-adjusted CI. If the mean difference is reported without individual group data, we will use this mean difference to report the study results. If more than one study measures the same outcome using different tools, we will calculate the standardised mean difference and 95% CI using the inverse variance method.

Unit of analysis issues

In a study with multiple intervention groups, we will combine all relevant experimental intervention groups into a single group to create a single pair-wise comparison (Higgins 2011).

Dealing with missing data

If trialists used intention-to-treat analysis to deal with missing data, we will use these data in our primary analysis. Otherwise, we will attempt to contact study authors to obtain missing data or we will use the data that are available to us.

Dealing with missing data using sensitivity analysis

If trials report only per protocol analysis results, we will include missing data by considering participants as treatment failures or treatment successes by imputing them according to the following two scenarios:

- 'extreme-case' analysis favouring the experimental intervention ('best-worse' case scenario): none of the participants who dropped out from the experimental group experienced the outcome, but all of the participants who dropped out from the control group experienced the outcome; including all randomised participants in the denominator;
- 'extreme-case' analysis favouring the control ('worst-best' case scenario): all participants who dropped out from the

experimental group, but none from the control group experienced the outcome; including all randomised participants in the denominator.

Assessment of heterogeneity

We will assess heterogeneity between the included studies using visual inspection of the forest plots. We will also assess statistical heterogeneity in each meta-analysis using the I^2 statistic and χ^2 test (Higgins 2003). We will regard heterogeneity as substantial if the I^2 statistic value is greater than 50%, or there is a low P value (less than 0.10) in the χ^2 test for heterogeneity (Deeks 2001; Higgins 2011). If there is substantial statistical heterogeneity, we will carry out subgroup analyses to assess differences between the included studies. However, if there are clinical, methodological, or remarkably high statistical heterogeneity (I^2 greater than 75%) across included studies, we will not report pooled results from meta-analysis, but we will instead use a narrative approach to data synthesis.

Assessment of reporting biases

We will examine funnel plots corresponding to meta-analysis of the primary outcome to assess the potential for small-study effects such as publication bias if more than 10 trials are identified. We plan to assess funnel plot asymmetry visually, and if asymmetry of funnel plots is identified, we will perform exploratory analyses to investigate it (Sterne 2011).

Data synthesis

Meta-analysis

We will perform the analysis using Review Manager 5 (RevMan 2014). We will perform meta-analysis using random-effects and fixed-effect models, and we will report the most conservative finding, using a P value of 0.025 or less, two-tailed, as statistically significant due to the three primary and three secondary outcomes (Jakobsen 2014). We will apply the eight-step procedure proposed by Jakobsen 2014 when assessing the statistical and clinical significance of the results of the meta-analyses.

Trial Sequential Analyses

We will apply Trial Sequential Analysis (Thorlund 2011) to minimise random errors in our meta-analysis (Brok 2008; Wetterslev 2008; Brok 2009; Thorlund 2009; Wetterslev 2009; Thorlund 2010; Wetterslev 2017). We will calculate the required information size (i.e. the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) which will also be accounted for the diversity observed in the meta-analysis (Wetterslev 2008; Wetterslev 2009; Wetterslev 2017).

We will calculate the required information size for dichotomous outcomes based on the event proportion in the control group; assumption of an a priori risk ratio reduction of 10% observed in the included trials; and the risk ratio reduction observed in trials at low risks of bias; a risk of type I error of 2.5% for both primary and secondary outcomes; a risk of type II error of 90%; and the assumed diversity of the meta-analysis. For continuous outcomes, we will estimate the required information size based on the standard deviation observed in the control group and a minimal relevant difference of 50% of this standard deviation, and the observed diversity in the trials in the meta-analysis.

We will add the trials according to the year of publication, and, if more than one trial has been published in a year, we will add trials alphabetically according to the last name of the first author. On the basis of the required information size, we will construct trial sequential monitoring boundaries (Wetterslev 2008; Thorlund 2011). These boundaries will determine the statistical inference that one may draw regarding the cumulative meta-analysis that has not reached the required information size; if the trial sequential monitoring boundary is crossed before the required information size is reached, firm evidence may perhaps be established and further trials may be superfluous. In contrast, if the boundary is not surpassed, it is most probably necessary to continue doing trials to detect or reject a certain intervention effect. That can be determined by assessing whether or not the cumulative Z-curve crosses the trial sequential monitoring boundary for futility (Wetterslev 2008). We will conduct Trial Sequential Analysis using software from The Copenhagen Trial Unit (Thorlund 2011; TSA 2011). For our meta-analyses using HRs, we will conduct robustness analyses by changing them into relative risk reduction as described above or use software that can handle HRs (Miladinovic 2013).

Subgroup analysis and investigation of heterogeneity

We will carry out subgroup analysis for the following factors.

- Trials at low risk of bias compared to trials at high risk of bias.
- Surgical margin status (histologically negative compared to histologically positive, regarding rest of cancer).
- Status of regional lymph node (negative compared to positive regarding cancer metastasis).
- Location of tumour (intrahepatic, perihilar, distal).
- Type of adjuvant chemotherapy (i.e. gemcitabine-based chemotherapy compared to similar chemotherapy without gemcitabine).

We will assess subgroup differences by interaction tests available within Review Manager 5 (RevMan 2014). We will report the

results of subgroup analyses quoting the Chi² statistic and P value, the interaction test, and I² statistic value.

Sensitivity analysis

We will apply 'best-worst case' and 'worst-best case' scenarios, when possible, to sensitivity analyses based on the outcomes of mortality and serious adverse events.

'Summary of findings' tables

We will create 'Summary of findings' tables on all review outcomes obtained from the included trials using GRADEpro software. We will also provide the review outcomes based on trials with low risk of bias in the 'Summary of findings' table. The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed (GRADEpro). The quality of a body of evidence considers within-study risk of bias, indirectness of the evidence, heterogeneity of the data, imprecision of effect estimates, and risk of publication bias (Balslem 2011; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2011h; Guyatt 2013a; Guyatt 2013b; Guyatt 2013c; Guyatt 2013d; Mustafa 2013; Guyatt 2017). We will evaluate imprecision using Trial Sequential Analysis as suggested by Jakobsen and colleagues (Jakobsen 2014).

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* Indicates the major publication for the study

APPENDICES

Appendix I. American Joint Committee staging for Cancer (AJCC) tumour-node metastasis (TNM) staging system for cholangiocarcinoma

Intrahepatic bile duct tumours	
Stage	Findings
0	Carcinoma in situ (intraductal tumour).
I	Solitary tumour without vascular invasion.
II	Solitary tumour with vascular invasion.
	Multiple tumours, with or without vascular invasion.
III	Tumour perforating the visceral peritoneum.
	Tumour involving local extrahepatic structures by direct invasion
IVA	Tumour with periductal invasion.
	Regional lymph node metastasis present.
IVB	Distant metastasis present.

(Continued)

Perihilar bile duct tumours	
Stage	Findings
0	Carcinoma in situ.
I	Tumour confined to the bile duct, with extension up to the muscle layer or fibrous tissue
II	Tumour invaded beyond the wall of the bile duct to surrounding adipose tissue
	Tumour invaded adjacent hepatic parenchyma.
IIIA	Tumour invaded unilateral branches of the portal vein or hepatic artery
IIIB	Regional lymph node metastasis (including nodes along the cystic duct, common bile duct, hepatic artery, and portal vein)
IVA	Tumour invades main portal vein or its branches bilaterally; or the common hepatic artery; or the second-order biliary radicals with contralateral portal vein or hepatic artery involvement
IVB	Metastasis to periaortic, pericaval, superior mesenteric artery, celiac artery lymph nodes, or a combination of these
	Distant metastasis present.
Distal bile duct tumours	
Stage	Findings
0	Carcinoma in situ.
IA	Tumour confined to the bile duct histologically.
IB	Tumour invaded beyond the wall of the bile duct.
IIA	Tumour invaded the gallbladder, pancreas, duodenum, or other adjacent organs without involvement of the celiac axis, or the superior mesenteric artery
IIB	Regional lymph node metastasis.
III	Tumour involves the celiac axis or superior mesenteric artery
IV	Distant metastasis.

Appendix 2. Search strategies

Database	Time span	Search strategy
The Cochrane Hepato-Biliary Group Controlled Trials Register	Date of search	((adjuvant or adjunct*) and (chemotherap* or drug* or therap*)) and (cholangiocarcinom* or (bile duct and (cancer* or carcinom* or malignan* or neoplasm* or tumor*)))
Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	Latest issue	#1 MeSH descriptor: [Chemotherapy, Adjuvant] explode all trees #2 (adjuvant or adjunct*) and (chemotherap* or drug* or therap*) #3 #1 or #2 #4 MeSH descriptor: [Cholangiocarcinoma] explode all trees #5 MeSH descriptor: [Bile Duct Neoplasms] explode all trees #6 cholangiocarcinom* or (bile duct and (cancer* or carcinom* or malignan* or neoplasm* or tumor*)) #7 #4 or #5 or #6 #8 #3 and #7
MEDLINE (OvidSP)	1946 to the date of search	1. exp Chemotherapy, Adjuvant/ 2. ((adjuvant or adjunct*) and (chemotherap* or drug* or therap*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. 1 or 2 4. exp Cholangiocarcinoma/ 5. exp Bile Duct Neoplasms/ 6. (cholangiocarcinom* or (bile duct and (cancer* or carcinom* or malignan* or neoplasm* or tumor*))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 7. 4 or 5 or 6 8. 3 and 7 9. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 10. 8 and 9
Embase (OvidSP)	1974 to the date of search	1. exp adjuvant chemotherapy/ 2. ((adjuvant or adjunct*) and (chemotherap* or drug* or therap*)).mp. [mp=title, abstract, heading word, drug trade

(Continued)

		name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 3. 1 or 2 4. exp bile duct tumor/ 5. (cholangiocarcinom* or (bile duct and (cancer* or carcinom* or malignan* or neoplasm* or tumor*))).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 6. 4 or 5 7. 3 and 6 8. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 9. 7 and 8
LILACS (Bireme)	1982 to the date of search	((adjuvant or adjunct\$) and (chemotherap\$ or drug\$ or therap\$)) [Words] and (cholangiocarcinom\$ or (bile duct and (cancer\$ or carcinom\$ or malignan\$ or neoplasm\$ or tumor\$))) [Words]
Science Citation Index Expanded (Web of Science)	1900 to the date of search	#5 #4 AND #3 #4 TS=(random* or blind* or placebo* or meta-analys*) #3 #2 AND #1 #2 TS=(cholangiocarcinom* or (bile duct and (cancer* or carcinom* or malignan* or neoplasm* or tumor*))) #1 TS=((adjuvant or adjunct*) and (chemotherap* or drug* or therap*))

CONTRIBUTIONS OF AUTHORS

VL: conceived the review question, developed, co-ordinated, and completed the protocol.

ES: conceived the review question, developed, and completed the protocol.

AP: developed and completed the protocol.

CK: developed, co-ordinated, and completed the protocol.

PL: developed, co-ordinated, edited the protocol, and advised on the protocol.

SK: developed and completed the protocol.

PP: edited part of the protocol and advised on part of the protocol.

All authors approved the publication of the current version.

DECLARATIONS OF INTEREST

VL: none known.

ES: none known.

AP: none known.

CK: none known.

PL: none known.

SK: none known.

PP: none known.

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Internal sources

- Department of Surgery, Faculty of Medicine, Khon Kaen University, Thailand.
- Department of Obstetrics and Gynaecology, Faculty of Medicine, Khon Kaen University, Thailand.
- Department of Biostatistics and Demography, Faculty of Public Health, Khon Kaen University, Thailand.
- Cochrane Thailand, Thailand.
- Cancer Unit, Faculty of Medicine, Khon Kaen University, Thailand.

External sources

- Thailand Research Fund (Distinguished Professor Award), Thailand.



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Nerve-sparing radical hysterectomy compared to standard radical hysterectomy for women with early stage cervical cancer (stage Ia2 to IIa) (Protocol)

Kietpeerakool C, Aue-aungkul A, Galaal K, Ngamjarus C, Lumbiganon P

Kietpeerakool C, Aue-aungkul A, Galaal K, Ngamjarus C, Lumbiganon P.

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
BACKGROUND	1
OBJECTIVES	3
METHODS	3
ACKNOWLEDGEMENTS	7
REFERENCES	7
APPENDICES	10
CONTRIBUTIONS OF AUTHORS	15
DECLARATIONS OF INTEREST	16
SOURCES OF SUPPORT	16

Nerve-sparing radical hysterectomy compared to standard radical hysterectomy for women with early stage cervical cancer (stage Ia2 to IIa)

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To evaluate the efficacy and safety of nerve-sparing radical hysterectomy in adult women with stage Ia2 to IIa cervical cancer.

BACKGROUND

Description of the condition

Cervical cancer remains a major health burden, with an age-standardised incidence rate (ASR) of 14.0 per 100,000 person-years (Ferlay 2015). In 2012, there were an estimated 528,000 new cases worldwide (Ferlay 2015). Approximately 85% of the global burden and nine out of ten (87%) cervical cancer deaths occur in low- and/or middle-income countries (Ferlay 2015). This high rate of cervical cancer-related death in these countries is mainly due to deficiencies in surveillance systems (Parkin 2014). Treatment for cervical cancer depends on the clinical stage of the disease. Staging of cervical cancer (processes carried out to find out how far the cancer has spread) is based on clinical findings obtained from

physical examination and diagnostic tests, which are used to assess the size of cervical mass, invasion into the tissues surrounding the cervix, and the spread to lymph nodes or distant organs (FIGO Committee 2014). The International Federation of Gynecology and Obstetrics (FIGO) staging system for cervical cancer is provided in Appendix 1 (FIGO Committee 2014).

A radical hysterectomy (also known as a Wertheim's hysterectomy) is performed to remove the uterus (womb), cervix, upper vagina and the parametria (tissues surrounding the cervix and upper vagina) (Verleye 2009; Marin 2014). Radical hysterectomy in conjunction with bilateral pelvic lymphadenectomy (the surgical removal of the lymph nodes found in the pelvis) is the standard surgical treatment for FIGO stage Ia2-IIa cervical cancer, when preservation of fertility is not required or advisable (Verleye 2009), although more limited treatment, such as cone biopsy (removal of a cone shaped piece of tissue from the cervix) or simple hysterectomy

tomy, with lymph node dissection, is increasingly considered for small volume disease. Concurrent chemoradiation (combination of drug and radiotherapy given at the same time) is also acknowledged as a standard treatment option for women with early stage cervical cancer (Vale 2010). Decision-making is based on individual patient characteristics and preferences, as well as weighing up the surgical risks with the longer-term risks of chemoradiation. Radical hysterectomy can be performed via laparotomy (open surgery), laparoscopic or robotic techniques (types of less invasive surgery). At present, there are three standard classification systems for radical hysterectomy (Marin 2014; Verleye 2009), including the Piver-Rutledge-Smith classification (Piver 1974), Querleu and Morrow classification (Querleu 2008), and the Gynecological Cancer Group of the European Organization for Research and Treatment of Cancer (GCG-EORTC) classification (Mota 2008) (See Appendix 2).

Five-year survival rates of women undergoing radical hysterectomy for stage Ia2 to IIa cervical cancer are over 80% (Hongladaromp 2014; Kim 2000; Mahawerawat 2013; Srisomboon 2011; Suprasert 2010). The procedure can, however, result in significant long-term complications (Laterza 2015; Manchana 2009; Suprasert 2010). Bladder dysfunction, caused by the disruption of the pelvic autonomic nerves during resections of parametria and paracolpium (the tissues surrounding the vagina), can be a major, distressing complication and may occur in up to 70% of women following radical hysterectomy (Laterza 2015; Plotti 2011; Suprasert 2010). Early postoperative bladder dysfunction includes a significant reduction of maximal urethral closure pressure (MUCP), increased volume of postvoid residual urine, detrusor muscle underactivity and diminished bladder sensation, which, in some cases, may require prolonged urethral catheterisation. Late postoperative bladder dysfunction involves a persistent reduction of MUCP, voiding with abdominal straining, high volume of postvoid residual urine, detrusor muscle over-activity, and stress urinary incontinence (loss of urine caused by physical stress, e.g. sneezing or jumping) with estimates ranging from 8% to 47% (Katepoom 2014; Laterza 2015).

Description of the intervention

The uterus, upper vagina, bladder and rectum receive innervation from both the sympathetic and parasympathetic supplies of the autonomic nervous system. These nerves control smooth muscle function and pain sensation in viscera (internal organs). The sympathetic supply arises from T11-L2 nerve roots, which form a branching network called the superior hypogastric plexus (also referred to as the presacral nerve). The superior hypogastric plexus enters the pelvis, dividing into right and left hypogastric nerves. The pelvic splanchnic nerve is formed from parasympathetic fibres from S2-S4 nerve roots. The pelvic splanchnic nerve merges with the hypogastric nerve to form left and right inferior hypogastric plexuses, which travel via the uterosacral ligaments (tissues that

connect between the posterior-lower part of the uterus to the anterior aspect of the sacrum) where they branch to supply the uterus and bladder (Fujii 2007; Huber 2015).

In terms of urinary function, the sympathetic nervous system relaxes the bladder muscle (detrusor muscle) to increase bladder capacity and constricts the internal urethral sphincter to inhibit the micturition (bladder voiding) reflex. The parasympathetic nervous system stimulates a series of contractions of the bladder muscle and relaxes the internal urethral sphincter (muscle that acts as a valve to control the exit of urine from the bladder), resulting in voluntary urination (Laterza 2015).

Nerve-sparing radical hysterectomy is a modified radical hysterectomy, developed to permit surgical removal (resection) of oncologically relevant tissues surrounding the cervical lesion, while preserving pelvic autonomic nerves (Charoenkwan 2010; Fujii 2008; Kato 2003). During nerve-sparing radical hysterectomy, parametrial dissection is carried out under directed visualisation of the adjacent pelvic autonomic nerves. Fibres of the hypogastric nerve can be identified in the mesoureter (tissues surrounding the ureter), approximately 2 cm to 3 cm beneath the ureter (tubes that carry urine from kidneys to the bladder). To minimise the risk of accidental transection (severing), the hypogastric nerve is partly dissected away from the level of resection of the posterior parametrium. During resection of the lateral parametrium, the inferior hypogastric plexus is directly visualised, partly dissected and separated to avoid disruption during resection. The vesical branch of inferior hypogastric plexus can be identified by following the course of the inferior hypogastric plexus from the uterosacral ligaments and is separated from the blood vessels of the tissue surrounding the vagina during resection of the anterior parametrium (Charoenkwan 2006; Charoenkwan 2010; Fujii 2007; Fujii 2008).

Nerve-sparing radical hysterectomy appears safe and feasible without compromising the extent of resection and the rate of cancer recurrence when compared to the standard techniques of radical hysterectomy (Charoenkwan 2006; Xue 2016). A factor predicting the likelihood of the success of nerve-sparing radical hysterectomy is the FIGO stage of the disease. Women with stage Ib1 cervical cancer are more likely to have successful preservation of autonomic nerves during laparoscopic nerve-sparing radical hysterectomy than those with a higher stage of disease (stage Ib2 to IIa) (Kim 2015).

How the intervention might work

The extent of potential injury to pelvic autonomic nerves is associated with the extent of the operation (Butler-Manuel 2000; Ercoli 2003). The surgical steps of radical hysterectomy that potentially damage the pelvic autonomic nerves are the resection of parametrial tissues, particularly posterior and anterior parametria (Ercoli 2003). Previous quantitative immunocytochemistry studies (postoperative examination of tissue removed during surgery

using antibodies to highlight nerve fibres when viewed under a microscope) indicated that the presence of nerve trunks (the main stem of a nerve), autonomic ganglia (nerve connection hubs), and free nerve fibres within the parametrial tissues, which were accidentally transected during conventional radical hysterectomy (Butler-Manuel 2000; Ercoli 2003; Maas 2005; Mantzaris 2008). In addition, when a more careful approach is used during resection of the parametria, through identification and isolation of the adjacent pelvic autonomic nerves, significantly fewer autonomic nerves are disrupted iatrogenically (inadvertently) during nerve-sparing radical hysterectomy than in conventional radical hysterectomy (Maas 2005; Mantzaris 2008). This results in a substantial reduction in nerve disruption and may lower the risk of developing bladder dysfunction after radical hysterectomy (Charoenkwan 2010; Fujii 2007; Tseng 2012).

Why it is important to do this review

Although the survival outcomes of women undergoing standard radical hysterectomy with pelvic lymphadenectomy for stage Ia2 to IIa cervical cancer are generally good, bladder dysfunction following standard radical hysterectomy can affect quality of life (QoL) significantly (Ceccaroni 2012; Wu 2010). Nerve sparing radical hysterectomy may offer improved QoL. However, there is the potential that a nerve-sparing approach may compromise oncological outcomes and increase the risk of disease recurrence. We aim to assess the benefits and harms of this approach in order to inform women and their surgeons about whether a more refined surgical approach is warranted, or whether a more traditional radical resection is to be recommended.

OBJECTIVES

To evaluate the efficacy and safety of nerve-sparing radical hysterectomy in adult women with stage Ia2 to IIa cervical cancer.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs).

Types of participants

Women aged 18 years or older undergoing radical hysterectomy (Piver class III, Querleu and Morrow type C, or GCG-EORTC type III) for stage Ia2 to IIa cervical cancer. [Appendix 1](#) and [Appendix 2](#) display the details of the FIGO staging classification of cervical cancer, and the classifications of radical hysterectomy, respectively. If studies include other stages of cervical cancer, we will contact trial authors to retrieve data related to the women with stage Ia2 to IIa cervical cancer only. If this is not possible, we will only include studies where at least 80% of participants were diagnosed with stage Ia2 to IIa cervical cancer.

Types of interventions

RCTs comparing nerve-sparing radical hysterectomy with pelvic lymphadenectomy versus standard radical hysterectomy with pelvic lymphadenectomy for cervical cancer stage Ia2 to IIa (See [Description of the intervention](#) for details of the differences between the two surgical interventions).

Types of outcome measures

Primary outcomes

- Overall survival: survival until death from all causes. Survival will be assessed from the time when women were enrolled in the study.
- Rate of intermittent self-catheterisation (ISC) at one month after the operation.
- QoL: assessed using a scale that has been validated through reporting of norms in a peer-reviewed publication, i.e. European Organization for Research and Treatment of Cancer (EORTC) QLQ-CX24 cervical cancer-specific QoL questionnaire (Greimel 2006).

Secondary outcomes

- Time to postvoid residual volume of urine ≤ 50 mL after operation (days) (amounts of urine measured by clean intermittent catheterisation after the patient feels as though bladder is empty).
- Postvoid residual volume of urine at 1 month, 3 months, 6 months, and 12 months after operation (mL).
- Adverse events (excluding bladder dysfunction): we will categorise the severity of the following adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE 2010): febrile morbidity; surgical site infections; genitourinary complications (e.g. fistula, hydronephrosis, vaginal stenosis); gastrointestinal complications (e.g. fistula, constipation); lymphovascular complications (e.g. lymphocyst, lymphoedema, thrombosis, embolism); direct surgical morbidity

(e.g. injury to bladder, ureter, small bowel or colon); reoperation (an operation to correct a condition not corrected by a previous operation or to correct the complications of a previous operation); readmission (a hospitalisation that occurs within 30 days after discharge from hospital); blood component transfusion (the transfer of blood or blood components from one person (the donor) into the bloodstream of another person (the recipient)).

- Subjective urinary symptoms: using a standard questionnaire, i.e. International Prostate Symptom Score (IPSS) (Barry 1992)
- Disease-free survival (DFS): survival until the appearance of a new lesion of disease. Survival will be assessed from the time when women are enrolled in the study.
- Rate of cancer recurrence: we will classify recurrences as loco-regional or distant.
- Rate of urinary tract infection during the month after operation diagnosed by cultivation of urine.
- Maximal urethral closure pressure (MUCP) from urodynamic measurements (cmH₂O).
- Maximum flow rate (mL per second) and number of women with low maximum flow rate (< 15 mL per second) obtained urodynamic measures.
- Detrusor pressure at maximum flow and number of women with low detrusor pressure at maximum flow (< 25 cmH₂O).
- Sexual dysfunction: using a validated scale, i.e. Sexual function-Vaginal change Questionnaire (SVQ) (Jensen 2004).
- Cost-effectiveness: using a validated scale, i.e. European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) (Cherny 2015).
- Operative time (minutes).
- Estimated blood loss (mL).
- Subjective urinary symptoms: using a standard questionnaire, i.e. International Prostate Symptom Score (IPSS) (Barry 1992)
- Disease-free survival (DFS): survival until the appearance of a new lesion of disease. Survival will be assessed from the time when women are enrolled in the study.
- Rate of cancer recurrence: we will classify as loco-regional and distant recurrences.
- Rate of urinary tract infection during the month after operation diagnosed by cultivation of urine.
- Maximal urethral closure pressure (MUCP) from urodynamic measurements (cmH₂O).
- Maximum flow rate (mL per second) and number of women with low maximum flow rate (< 15 mL per second) obtained urodynamic measures.
- Detrusor pressure at maximum flow and number of women with low detrusor pressure at maximum flow (< 25 cmH₂O).
- Sexual dysfunction: using a validated scale, i.e. Sexual function-Vaginal change Questionnaire (SVQ) (Jensen 2004).
- Cost-effectiveness: using a validated scale, i.e. European Society for Medical Oncology Magnitude of Clinical Benefit

Scale (ESMO-MCBS) (Cherny 2015).

- Operative time (minutes).
- Estimated blood loss (mL).

We plan to present a 'Summary of findings' table to report the following outcomes listed in order of priority (see Appendix 3;

Data synthesis):

- overall survival;
- rate of ISC one month after operation;
- time to postvoid residual volume of urine $\leq$ 50 mL after operation;
- postvoid residual volume of urine one month after operation;
- rate of adverse event excluding bladder dysfunction;
- disease-free survival;
- QoL.

Search methods for identification of studies

We will include RCTs, irrespective of the language of publication, publication status or sample size.

Electronic searches

We will search the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL, latest issue);
- MEDLINE (1946 to present date);
- Embase (1980 to present date).

The Ovid MEDLINE search strategy is presented in Appendix 4. For databases other than MEDLINE, we will adapt the search strategy accordingly. All relevant articles will be identified on PubMed and we will make a further search for newly published articles using the 'related articles' feature.

Searching other resources

Ongoing trials and grey literature

We will search the World Health Organization's International Clinical Trials Registry Platform (www.who.int/ictrp/en) and ClinicalTrials.gov to identify any ongoing trials. If we identify ongoing trials that have not been published, we plan to approach the principal investigators and major co-operative groups active in this area, to ask for relevant data. We will search the following databases for grey literature: Open Grey (www.opengrey.eu) and Index to Theses (ProQuest Dissertations & Theses: UK & Ireland).

Handsearching

We will handsearch the citation lists of included studies, key textbooks and previous systematic reviews, and we plan to contact experts in the field to identify further reports of trials. We will also handsearch the reports of conferences from the following sources (from the year when electronic conference proceedings became available to current):

- Annual Meeting of the American Society of Gynecologic Oncology;
- Annual Meeting of the European Society of Medical Oncology;
- Annual Meeting of the American Society of Clinical Oncology;
- Annual Meeting of the British Gynaecological Cancer Society;
- Biennial Meeting of the Asian Society of Gynecologic Oncology;
- Biennial Meeting of the Asia and Oceania Federation of Obstetrics and Gynaecology;
- Biennial Meeting of the European Society of Gynaecological Oncology; and
- Biennial Meeting of the International Gynecologic Cancer Society.

Data collection and analysis

Selection of studies

We will download all titles and abstracts retrieved by electronic searching to a reference management database ([EndNote](#)). After duplicates are removed, we will transfer these data to [Covidence](#) (www.covidence.org). We plan to exclude those studies that clearly do not meet the inclusion criteria and we will obtain copies of the full text of potentially relevant references. Independently, two review authors (CK and AA) will assess the eligibility of the retrieved reports/publications. We will resolve any disagreement through discussion or, if required, we will consult a third person (KG or PL). We will identify and exclude duplicates and collate multiple reports of the same study. We will use the details regarding the selection process in Covidence to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table ([Liberati 2009](#)).

Data extraction and management

Two review authors (CK and AA) will independently extract study characteristics and outcome data from included studies. We plan to note when outcome data are not reported in a usable way in the 'Characteristics of included studies' table. We intend to resolve disagreements by consensus or by involving a third person (KG or PL).

For included studies, we will extract the following data.

- Author, year of publication and journal citation (including language)
- Country
- Setting
- Inclusion and exclusion criteria
- Study design and methodology
- Study population and disease characteristics
 - Total number enrolled
 - Participant characteristics
 - Age
 - Co-morbidities
 - Other baseline characteristics
 - Surgical technique (laparotomy, laparoscopy or robotic-assisted procedure)
 - Estimated blood loss (mL)
 - Stage of cervical cancer
 - Histopathological subtype of cervical cancer
 - Tumour size (largest tumour diameter)
 - Lymphadenectomy details including technique (sampling versus complete dissection) and status of lymph nodes (negative or positive for metastasis)
 - Radicality of the operation
 - Operative time (minutes)
 - Postoperative adjuvant treatment received and indication
- Intervention details
 - Nerve-sparing radical hysterectomy
- Comparison
 - Conventional radical hysterectomy
- Risk of bias in study (see below)
- Duration of follow-up
- Outcomes: for each outcome, we will extract the outcome definition and unit of measurement (if relevant). For adjusted estimates, we will record variables adjusted for in analyses.
 - Results: we will extract the number of participants allocated to each intervention group, the total number analysed for each outcome and the missing participants.
 - Notes: funding for trial and notable conflicts of interest of trial authors.

We will extract results as follows.

- For time-to-event data (survival outcomes and time to post void residual urine ≤ 50 mL after operation), we will extract the log of the hazard ratio (log(HR)) and its standard error from trial reports. If these are not reported, we plan to estimate the log (HR) and its standard error using the methods of [Parmar 1998](#).
- For dichotomous outcomes (e.g. adverse events and urinary tract infection), we will extract the number of women in each treatment arm who experienced the outcome of interest and the number of women assessed at endpoint, in order to estimate a risk ratio (RR).
- For continuous outcomes (e.g. time to postvoid residual urine ≤ 50 mL after operation, volume of postvoid residual

urine and QoL measures), we will extract the final value and standard deviation of the outcome and the number of women assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference between treatment arms (if trials measured outcomes on the same scale) or standardised mean difference (if trials measured outcomes on different scales) between treatment arms and its standard error.

Where possible, we intend to extract data according to an intention-to-treat analysis, in which participants will be analysed in the groups to which they were assigned.

Assessment of risk of bias in included studies

We will assess and report on the methodological quality and risk of bias of included studies in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), which recommends the explicit reporting of the following individual issues for RCTs.

- Selection bias: random sequence generation and allocation concealment
- Performance bias: blinding of participants and personnel (participants and outcome assessors)
- Detection bias: blinding of outcome assessment
- Attrition bias: incomplete outcome data (i.e. incomplete follow-up outcomes and treatment-related complications)
- Reporting bias: selective reporting of outcomes
- Other potential bias

Two review authors (CK and AA) will apply the 'Risk of bias' tool independently and resolve differences by discussion or by appeal to a third review author (KG or PL). We will judge each item as being at high, low or unclear risk of bias as set out in the criteria displayed in Appendix 5 (Higgins 2011). We will provide a quote from the study report or a statement (or both) as justification for the judgement for each item in the 'Risk of bias' table. We will summarize the results in both a 'Risk of bias' graph and a 'Risk of bias' summary. When interpreting treatment effects and meta-analyses, we will take into account the risk of bias for the studies that contributed to that outcome. Where information on risk of bias relates to unpublished data, or correspondence with a trialist, we plan to note this in the table.

Measures of treatment effect

We plan to use the following measures of the effect of treatment.

- For time-to-event outcomes (survival outcomes and time to postvoid residual urine ≤ 50 mL after operation), we plan to use hazard ratios (HR) with 95% confidence intervals (CI).
- For dichotomous outcomes (e.g. adverse events and urinary tract infection) we plan to analyse data on the basis of the number of events and number of people assessed in the intervention and comparison groups. We will use these to calculate the RR and 95% CI.

- For continuous outcomes (e.g. volume of postvoid residual urine and QoL measures), we plan to analyse data based on the mean, standard deviation (SD) and number of people assessed for both the intervention and comparison groups to calculate the mean difference (MD) between treatment arms with a 95% CI. If the MD is reported without individual group data, we intend to use this to report the study results. If more than one study measures the same outcome using different tools, we plan to calculate the standardised mean difference (SMD) and 95% CI using the inverse variance method.

Unit of analysis issues

The units of analysis are the participants receiving interventions of interest. A study with multiple intervention groups is not applicable for this review, as we plan to compare the two interventions, namely nerve-sparing radical hysterectomy versus standard radical hysterectomy.

Dealing with missing data

We will not impute missing outcome data for any of the outcomes. We plan to attempt to contact study authors to obtain missing data.

Assessment of heterogeneity

We will assess clinical heterogeneity by visual inspection of the forest plots. Also, we will assess statistical heterogeneity in each meta-analysis using the I^2 statistic and χ^2 test (Deeks 2001; Higgins 2011). We plan to perform subgroup analysis to investigate the potential heterogeneity of the included studies, if feasible. If there is evidence of substantial clinical and methodological heterogeneity across the included studies, we plan to apply a narrative review approach to data synthesis.

Assessment of reporting biases

We intend to examine funnel plots corresponding to meta-analysis of the primary outcome to assess the potential for small study effects such as publication bias, if we identify more than 10 studies. We plan to assess funnel plot asymmetry visually (Sterne 2011).

Data synthesis

We will carry out statistical analysis using Cochrane Review Manager 5 software (Review Manager 2014). We will use the random-effects model with inverse variance weighting for all meta-analyses (DeSimonian 1986).

- For time-to-event data, we plan to pool hazard ratios using the generic inverse variance method.
- For any dichotomous outcomes, we plan to calculate the risk ratio (RR) for each study and then pool these.

- For continuous outcomes, we plan to pool the mean differences (MD) between the treatment arms, if all trials measure the outcome on the same scale; otherwise we plan to pool standardised mean differences (SMD).

Main outcomes of 'Summary of findings' table for assessing the quality of the evidence

Appendix 3 displays a 'Summary of findings' table, which we have prepared to summarize the results of the meta-analysis based on the methods described in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011).

We will present the results of meta-analysis and overall quality of the evidence for seven main outcomes as outlined in [Types of outcome measures](#) according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which will take into account issues not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias), but also to external validity such as directness of results (Langendam 2013). We will create a 'Summary of findings' table using GRADEpro GDT (www.grade.pro.org). We will downgrade the evidence from high quality by one level for each serious limitation, or by two levels for any very serious limitation. The GRADE levels of evidence can be interpreted as shown below.

- **High quality:** the true effect lies close to that of the estimate of the effect.
- **Moderate quality:** the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low quality:** the true effect may be substantially different from the estimate of the effect.
- **Very low quality:** the true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

We will carry out subgroup analysis for the following factors.

- Surgical approach technique (laparotomy versus minimally-invasive approach i.e. laparoscopy, robotic-assisted technique)
- Stage of the disease (Ia2-Ib1 versus Ib2 or higher stages)
- Degree of lymph node dissection: pelvic versus pelvic and para-aortic

We will assess subgroup differences by interaction tests available within Review Manager 5 (Review Manager 2014). We will report the results of subgroup analyses quoting the Chi² statistic and P value, the interaction test, and I² statistic values.

Sensitivity analysis

For all outcomes for which pooling are feasible, we will perform sensitivity analyses to determine the robustness of the findings by:

- repeating the analysis excluding any unpublished studies;
- repeating the analysis excluding RCTs judged to be at high or unclear risk of bias for allocation concealment.
- repeating the analysis excluding RCTs that contained women with cervical cancer other than stage Ia2 to IIa

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* Indicates the major publication for the study

APPENDICES

Appendix I. The International Federation of Gynecology and Obstetrics (FIGO) staging for carcinoma of the cervix

FIGO Stage			Description
I			The carcinoma is confined to the cervix.
	IA		Invasive cancer identified only microscopically. (All gross lesions even with superficial invasion are Stage IB cancers.) Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm
		IA1	Measured invasion of stroma ≤ 3 mm in depth and ≤ 7 mm width
		IA2	Measured invasion of stroma > 3 mm and < 5 mm in depth and ≤ 7 mm width
	IB		Clinical lesions confined to the cervix, or preclinical lesions greater than stage IA
		IB1	Clinical lesions no greater than 4 cm in size
		IB2	Clinical lesions > 4 cm in size
II			The carcinoma extends beyond the uterus, but has not extended onto the pelvic wall or to the lower third of vagina
	IIA		Involvement of up to the upper two-thirds of the vagina. No obvious parametrial involvement
		IIA1	Clinically visible lesion ≤ 4 cm

(Continued)

	IIA2	Clinically visible lesion > 4 cm
	IIB	Parametrial involvement, but not onto the pelvic sidewall
III		The carcinoma has extended onto the pelvic sidewall. On rectal examination, there is no cancer free space between the tumour and pelvic sidewall. The tumour involves the lower third of the vagina. All cases of hydronephrosis or non-functioning kidney should be included unless they are known to be due to other causes
	IIIA	Involvement of the lower vagina but no extension onto pelvic sidewall
	IIIB	Extension onto the pelvic sidewall, or hydronephrosis/non-functioning kidney
IV		The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum
	IVA	Spread to adjacent pelvic organs
	IVB	Spread to distant organs

Appendix 2. Classifications of radical hysterectomy

Piver-Rutledge-Smith (Piver 1974)	Extent of surgery
Class I: extrafascial hysterectomy	• Identification of ureters to avoid injury • Uterine vessels are resected and ligated close to the uterine isthmus • Uterosacral and cardinal ligaments are not removed • No vaginal portion is excised
Class II: modified radical hysterectomy (Wertheim)	• Ureters are dissected in the paracervical tissues but are not separated from the pubovesical ligament • Uterine arteries are resected and ligated beside and medial the ureter • Uterosacral and cardinal ligaments are excised up to the medial half portions • Vagina is excised up to the upper third level • Pelvic lymphadenectomy
Class III: classical radical hysterectomy (Meigs)	• Complete dissection of ureters from the pubovesical ligament except for the small part where the umbilical bladder artery is located to the level of their penetration into the bladder • Uterine arteries are cut off at the origin • Uterosacral and cardinal ligaments are resected as close to sacral insertion and pelvic side wall, respectively • Vagina is removed up to the upper half level

(Continued)

Class IV	Class IV differs from the Class III according to the following issues; • Complete dissections of the ureters from the pubovesical ligament • Umbilical artery is sacrificed • Vagina is removed up to the three-quarters level	
Class V	Class V differs from Class IV with the addition of the excision of a portion of the ureter or bladder which is involved by the tumour	
Querleu and Morrow (Querleu 2008)	Extent of surgery	
Type A: minimum resection of paracervix (extrafascial hysterectomy)	• The position of ureters are determined by palpation or direct vision without freeing from their beds • The paracervix is transected medial to the ureter but lateral to the cervix • The uterosacral and vesicouterine ligaments are not transected at the distance from the uterus • Vaginal resection is at a minimum, generally less than 10 mm without removal of the paracolpos	
Type B: transection of paracervix at the ureter	B1	• Ureters are unroofed and dissected laterally, permitting transection of the paracervix at the level of the ureteral tunnel • The posterior and deep neural component of the paracervix caudal to the deep uterine vein is not resected • At least 10 mm of the vagina from the cervix or tumour is excised
	B2	• As described in B1 with additional removal of the lateral paracervical lymph nodes
Type C: transection of paracervix at junction with internal iliac vascular system	C1	• Uterosacral ligament is transected at the sacral insertion • Vesicouterine ligament is transected at the bladder • Ureters are mobilised completely • Vagina is excised at least 15-20 mm from the tumour and the corresponding paracolpos is resected routinely • WITH the preservation of the autonomic nerves
	C2	• As described in C1 but WITHOUT the preservation of the autonomic nerves
Type D: Laterally extended resection	D1	• Resection of the entire paracervix at the pelvic side wall along with the hypogastric vessels, exposing the roots of the sciatic nerve • Total resection of the vessels of the lateral part of the paracervix
	D2	• As described in D1 plus resection of the entire paracervix with the hypogastric vessels and adjacent fascia and muscles
GCG-EORTC ^a (Mota 2008)	Extent of surgery	

(Continued)

Type I	Simple hysterectomy
Type II: modified radical hysterectomy ^b	• The uterus, paracervix and upper vagina (10-20 mm) are removed after dissection of the ureters to the point of their entry to the bladder • Uterine arteries are cut off and ligated • Medial half of parametria and proximal uterosacral ligaments are transected
Type III: radical hysterectomy ^b	• En bloc removal of the uterus with the upper third of the vagina along with the paracervical and paravaginal tissues • Uterine arteries are cut off and ligated at their origin • The entire width of the parametria is resected bilaterally • The entire uterosacral ligament is resected
Type IV: extended radical hysterectomy ^b	• Differs from Type 3, as three-quarters of the vagina and paravaginal tissues are resected
Type V: partial exenteration ^b	• Terminal ureters or segments of bladder or rectum are resected along with the uterus and parametria

^a Gynecological Cancer Group of the European Organization for Research and Treatment of Cancer

^b in conjunction with a systematic bilateral pelvic lymphadenectomy

Appendix 3. 'Summary of findings' table

Title: Nerve-sparing radical hysterectomy compared to standard radical hysterectomy for women with early stage cervical cancer (stage Ia2 to IIa)						
Patient or population: women with stage Ia2 to IIa cervical cancer						
Settings: specialist hospital						
Intervention: nerve-sparing radical hysterectomy with pelvic lymph node dissection						
Comparison: standard radical hysterectomy with pelvic lymph node dissection						
Outcomes	Illustrative comparative risks*		Relative effect (95% CI)	Number of participants (studies)	Quality of evidence (GRADE)	Comment
	Assumed risk	Corresponding risk				
Overall survival						
Rate of ISC at 1 month after operation						
Time to postvoid residual volume						

(Continued)

of urine $\leq$ 50 mL after operation						
Postvoid residual volume of urine at 1 month						
Rate of adverse events (excluding bladder dysfunction)						
Disease-free survival						
Quality of life						
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; HR: hazard ratio; ISC: intermittent self-catheterisation; MD: mean difference; RR: risk ratio; OR: odds ratio						
GRADE Working Group grades of evidence High quality: further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: there is uncertain about the estimate.						

Appendix 4. MEDLINE Ovid search strategy

1. Uterine Cervical Neoplasms/
2. (cervi* adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*)).mp.
3. 1 or 2
4. exp Hysterectomy/
5. hysterectom*.mp.
6. ((uter* or womb) adj5 (remov* or excis*)).mp.
7. 4 or 5 or 6
8. Urinary Bladder/
9. Urinary Catheterization/
10. exp Urinary Bladder Diseases/
11. exp Lower Urinary Tract Symptoms/
12. exp Urination Disorders/
13. exp Urinary Tract Infections/
14. Urination/
15. ((bladder* or urethra* or ureter* or urin* or urologic*) adj5 (dysfunction* or disorder* or disease* or infect* or incontinence* or urgenc* or injur* or damage*)).mp.
16. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

Appendix 5. 'Risk of bias' assessment

'Risk of bias' assessment based on Chapter 8 of [Higgins 2011](#):

- Random sequence generation
 - Low risk of bias, e.g. participants assigned to treatments on the basis of a computer-generated random sequence or a table of random numbers.
 - High risk of bias, e.g. participants assigned to treatments on the basis of date of birth, clinic ID number or surname, or no attempt to randomise participants.
 - Unclear risk of bias, e.g. not reported, information not available.
- Allocation concealment
 - Low risk of bias, e.g. where the allocation sequence could not be foretold.
 - High risk of bias, e.g. allocation sequence could be foretold by patients, investigators or treatment providers.
 - Unclear risk of bias, e.g. not reported.
- Blinding of participants and personnel
 - Low risk of bias if participants and personnel were adequately blinded.
 - High risk of bias if participants were not blinded to the intervention that the participant received.
 - Unclear risk of bias if this was not reported or unclear.
- Blinding of outcomes assessors
 - Low risk of bias if outcome assessors were adequately blinded.
 - High risk of bias if outcome assessors were not blinded to the intervention that the participant received.
 - Unclear risk of bias if this was not reported or is unclear.
- Incomplete outcome data: we will record the proportion of participants whose outcomes were not reported at the end of the study. We will code a satisfactory level of loss to follow-up for each outcome as:
 - Low risk of bias, e.g. if fewer than 20% of participants were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms
 - High risk of bias, e.g. if more than 20% of participants were lost to follow-up or reasons for loss to follow-up differed between treatment arms.
 - Unclear risk of bias, e.g. if loss to follow-up was not reported.
- Selective reporting of outcomes
 - Low risk of bias, e.g. review reports all outcomes specified in the protocol.
 - High risk of bias, e.g. it is suspected that outcomes have been selectively reported in the study.
 - Unclear risk of bias, e.g. it is unclear whether outcomes have been selectively reported.
- Other bias
 - Low risk of bias, e.g. the review authors do not suspect any other source of bias and the trial appears to be methodologically sound.
 - High risk of bias, e.g. the review authors suspect that the trial was prone to an additional bias.
 - Unclear risk of bias, e.g. the review authors are uncertain whether an additional bias may have been present.

CONTRIBUTIONS OF AUTHORS

Chumnan Kietpeerakool (CK): conceived the review question, developed, co-ordinated and completed the protocol

Apiwat Aue-aungkul (AA): conceived the review question, developed, and completed the protocol

Khadra Galaal (KG): developed, and completed the protocol

Chetta Ngamjarus (CN): performed part of the editing of the protocol and advised on part of the protocol

Pisake Lumbiganon (PL): co-ordinated the development of the protocol, edited the protocol and advised on the protocol

DECLARATIONS OF INTEREST

CK: nothing to declare

AA: nothing to declare

KG: nothing to declare

CN: nothing to declare

PL: nothing to declare

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Internal sources

- Department of Obstetrics and Gynaecology, Faculty of Medicine, Khon Kaen University, Thailand.
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- Cochrane Thailand, Thailand.

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RESEARCH ARTICLE

Open Access

Maternal near-miss and mortality in Sayaboury Province, Lao PDR

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Abstract

Background: Maternal near-miss (MNM) incidence is the indicator reflecting maternal healthcare services. This study aimed to determine the burden of maternal near-miss and maternal deaths in Sayaboury Province, Lao PDR.

Methods: A descriptive study was done in a cohort of 1215 pregnant women, who had their last normal menstrual period (LMP) between 1 August and 31 December, 2010. WHO criteria for MNM were used to identify near-miss cases and maternal deaths during February – November 2011. Data of maternal characteristics, MNM, and maternal deaths were prospectively collected by primary health care workers in the villages under supervision of health staff in local health centers and by the head nurses of the gynecology - obstetric wards in the studied hospitals. Frequencies with 95% confidence intervals (CIs) were used to describe maternal near-misses and maternal deaths.

Results: Overall, 92.5% of the 1215 pregnancies were delivered, 7.5% were aborted. Eleven women were identified as near-miss cases, giving a maternal near miss (MNM) ratio of 9.8 (95% CI: 4.9 -17.5)/1,000 live births. With two maternal deaths, the maternal mortality ratio (MMR) was 178 (95% CI: 50–650)/100,000 live births. Together, these constituted 13 cases of severe maternal outcome (SMO) and given the SMO ratio of 11.6 (95% CI: 6.2 - 19.8)/1,000 live births.

Conclusion: The study shows a surprisingly low MNM ratio and MMR in Sayaboury Province, Lao PDR. Generalization of the results is limited by problems in applying standard criteria for the identification of near-misses in the communities and local hospitals. However, the findings are considered to have important implications for the improvement of maternal health services in low resource settings, e.g. to obtain valid and reliable maternal near miss and maternal deaths for the whole country.

Keywords: Maternal near- miss, Maternal mortality, Severe maternal outcome, Maternal complication

Background

The fifth Millennium Development Goal (MDG) is to improve maternal health. The two main targets for improvement are 1) to reduce the maternal mortality ratio (MMR) by three quarters between 1990 & 2015 and 2) to achieve universal access to reproductive health by 2015 [1,2]. Levels of maternal mortality have decreased, but the global maternal mortality ratio declined by only 2.3% per year between 1990 and 2008. This figure is far from what is required to achieve MDG 5 with the aim of an annual decline of 5.5% [1-3].

In spite of the efforts of international developments in maternal health care, maternal deaths and disabilities

remain a major public health problem in developing countries. Lack of reliable and up-to-date statistics on maternal deaths also remains a major challenge to the implementation of a master plan in the developing countries to accelerate achieving the Millennium Development Goal related to maternal health (MDG-5) [2-4]. There are 14 countries in the world which have MMR of at least 1,000 per 100,000 live births. In most developing countries where there is no comprehensive registration of deaths, reliability of maternal mortality ratios is still questionable because of lack of medical certification of death [1,4].

Maternal mortality is the health indicator which shows the greatest gap between the rich and poor countries. Whereas nine maternal deaths per 100,000 live births have been reported in developed countries, 450 maternal deaths per 100,000 live births occurred in developing

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countries. Approximately 13,000 maternal deaths occur annually in the Western Pacific Region, with large differences within developing countries (urban–rural, rich–poor) [5]. By region, the MMR is highest in Africa (830) and some countries of the Western Pacific Region, the Middle East, followed by Asia (330), Oceania (240), Latin America and the Caribbean (190), and is lowest in the developed countries [1,6,7]. In the Lao People's Democratic Republic, the MMR has been roughly estimated to be 400 – 600 for every 100,000 live births [4,8-10]. When compared with neighboring countries in South - East Asia, the maternal health indicators for Lao PDR are the worst in the region [5,8].

However, despite the high maternal morbidity ratios in many resource-poor settings, maternal deaths are still rare in absolute numbers [6]. The study of women who survive life-threatening complications related to pregnancy, called maternal near-miss cases, may represent a practical alternative to surveillance of maternal morbidity and mortality [11]. There have been no official reports of maternal near-miss in the Lao PDR. The Ministry of Health (MOH) of Lao PDR, in cooperation with international agencies, has recently made serious efforts to improve maternal and child health. They have attempted to reduce maternal mortality through implementing new or additional maternal and child health (MCH) service-related activities, such as trained traditional birth attendances (TBA) at the village, trained skill birth attendances (SBA) in the health centers, supported family planning and EPI etc. Despite the efforts, maternal health status was still relatively poor in some areas of the country, and major capacity strengthening is still required in the areas of poor MCH services for instance in mountainous remote areas. Official statistics on MCH indicators have been improving over the past decades, but they remain below international standards. The lack of reliable and up-to-date statistics on maternal deaths and morbidities remains a major challenge for achieving accelerated progress towards the Millennium Development Goal related to maternal health (MDG-5) [1,4,12].

Sayaboury Province is one of the remote, mountainous provinces located in the northwestern Lao PDR. Many villages in the remote areas have limited access to health services during the wet season, especially in the mountainous, remote villages. In its efforts to increase access through village health volunteers and the village revolving drug funds, the provincial health office (PHO) has managed to reach almost all villages in the province to provide primary health care [8,12]. An annual report of Sayaboury PHO 2009 showed that 39% of pregnant women delivered in the hospital and 61% delivered at home. Acute obstetric complications were problems for the women living in remote areas, where road access was still difficult. The referral system for pregnant women was

ill-equipped, especially when they were high risk for developing complications.

To address the quality of maternal healthcare services in a low resource setting, this study was conducted to determine the incidence and causes of maternal near-misses and deaths in Sayaboury Province, Lao PDR.

Methods

Population and setting

This was a population-based descriptive study to prospectively detect maternal near-misses and maternal deaths in four randomly selected districts from a total of eleven districts in Sayaboury Province during February – November 2011. Two hundred and forty three villages in these four districts were our study sites. These are small villages with a total population of 199,238 people and only 98,164 women. Pregnant women, who had their last normal menstrual period (LMP) between 1 August and 31 December, 2010, were recruited. The LMP range was chosen intending to have enough pregnant women based on the estimated sample size and to follow up the eligible women for their pregnancy outcomes (especially maternal near miss and maternal death). We also had information about those women who aborted before we started data collection from the records routinely collected by traditional birth attendants (TBAs). Exclusion criteria were women who planned to move out of the area during the study period. The eligible women were identified by trained village health volunteers (VHVs) and TBAs under the supervision of health center staff. In cases of uncertainty, pregnancy was confirmed by a urine dipstick test. Recruited pregnant women were home visited daily to detect complication by trained TBAs and VHVs, who lived in the same villages, over the study period. These were not antenatal care visits. They notified health center staff when pregnant women in their villages had abortion or delivery at home. If pregnant women with severe complications (such as severe haemorrhage, dystocia, hypertension etc.) were notified in the villages by trained TBAs or VHVs, the health center staff from the nearest health center went to investigate and confirm the diagnosis of a MNM using case record form (CRF) and referred serious cases to the nearest hospital, which on average was five to ten kilometers away from the village. However in mountainous areas it might take longer time to refer patients to the hospital.

Variables

The primary outcomes were maternal near-misses and maternal deaths. A maternal near-miss (MNM) was a woman who nearly died but survived a complication, which occurred during pregnancy, childbirth or within 42 days of termination of pregnancy. The modified WHO criteria of organ system dysfunctions [13] as shown in Table 1 were

Table 1 WHO criteria and modified WHO criteria of organ system dysfunctions for detection of maternal near miss (MNM)

WHO Criteria for MNM detection	Modified WHO criteria for MNM detection at hospital	Modified WHO criteria for MNM detection at community
1) Cardiovascular dysfunction Shock Cardiac arrest Severe hypoperfusion (lactate >5 mmol/L or >45mg/dL) Severe acidosis (pH<7.1) Use of continuous vasoactive drugs Cardio-pulmonary resuscitation	1) Cardiovascular dysfunction Shock Cardiac Arrest Severe hypoperfusion (lactate >5 mmol/L or >45 mg/dL) Severe acidosis (pH<7.1) Use of continuous vasoactive drugs Cardio-pulmonary resuscitation	1) Cardiovascular dysfunction Shock Cardiac Arrest
2) Respiratory dysfunction Acute cyanosis Gasping Severe tachypnea (respiratory rate>40 breaths per minute) Severe bradypnea (respiratory rate<6 breaths per minute) Severe hypoxemia (O2 saturation <90% for _60 min or PAO2/FiO2<200) Intubation and ventilation not related to anaesthesia	2) Respiratory dysfunction Acute cyanosis Gasping Severe tachypnea (respiratory rate>40 breaths per minute) Severe bradypnea (respiratory rate<6 breaths per minute) Severe hypoxemia (O2 saturation <90% for _60min or PAO2/FiO2<200) Intubation and ventilation not related to anaesthesia	2) Respiratory dysfunction Acute cyanosis Severe tachypnea (respiratory rate>40 breaths per minute) Severe bradypnea (respiratory rate<6 breaths per minute)
3) Renal dysfunction Oliguria non responsive to fluids or diuretics Severe acute azotemia (creatinine >300umol/ml or >3.5 mg/dL) Dialysis for acute renal failure	3) Renal dysfunction Oliguria non responsive to fluids or diuretics Severe acute azotemia (creatinine >300umol/ml or >3.5mg/dL) Dialysis for acute renal failure	3) Renal dysfunction Oliguria non responsive to fluids or diuretics
4) Coagulation dysfunction Failure to form clots Severe acute thrombocytopenia (<50,000 platelets/ml) Massive transfusion of blood or red cells (≥5 units)	4) Coagulation dysfunction Failure to form clots Severe acute thrombocytopenia (<50,000 platelets/ml) Massive transfusion of blood or red cells (≥5 units)	4) Coagulation/Hematologic dysfunction Excessive bleeding per vagina
5) Hepatic dysfunction Jaundice in the presence of pre-eclampsia Severe acute hyperbilirubinemia (bilirubin>100 umol/L or > 6.0 mg/dL)	5) Hepatic dysfunction Jaundice in the presence of pre-eclampsia Severe acute hyperbilirubinemia (bilirubin>100 umol/L or > 6.0 mg/dL)	5) Hepatic dysfunction Jaundice in the presence of pre-eclampsia
6) Neurologic dysfunction Prolonged unconsciousness or coma (lasting >12 hours) Stroke	6) Neurologic dysfunction Prolonged unconsciousness or coma (lasting >12 hours) Stroke	6) Neurologic dysfunction Prolonged unconsciousness or coma (lasting >12 hours) Stroke

Table 1 WHO criteria and modified WHO criteria of organ system dysfunctions for detection of maternal near miss (MNM) (Continued)

Uncontrollable fit/status epilepticus	Uncontrollable fit/status epilepticus	Global paralysis
Global paralysis	Global paralysis	
7) Uterine dysfunction	7) Uterine dysfunction	
Uterine infection or haemorrhage leading to hysterectomy	Uterine infection or haemorrhage leading to hysterectomy	

used for the identification of near-misses. Severe maternal outcomes (SMO) were also measured and defined as women who had problem with maternal death or maternal near-miss up to 42 days after giving birth or having an abortion irrespective of gestational age or delivery status.

Data collection

During February – November 2011, at communities information of pregnancy outcomes, and clinical criteria for the assessment of organ system dysfunctions, such as severe tachypnea (respiratory rate > 40 breaths per minute) or severe bradypnea (respiratory rate < 6 breaths per minute, etc. were collected by the trained health center staff using the pre-established case record form (CRF). All completed CRFs were sent to the head of the maternal and child health (MCH) district office for rechecking and then forwarded to the provincial MCH division. In cases of abortion, the completed CRFs were sent to the provincial MCH division together with a monthly report. Pregnant women, who were referred to the hospitals because of serious complications or intended to deliver their babies in the district or provincial hospital, were followed up until delivery or termination of pregnancy by responsible staff at the district and provincial hospitals.

At the district and provincial hospitals information of pregnancy outcomes and the assessment of clinical criteria, laboratory-based and management-based criteria of organ system dysfunctions of all pregnant women up to 7th day after delivery were collected by trained head of nurse in the gynecology-obstetric wards, and MCH staff at health center or VHV in the village continued to follow-up these women until 42 days after delivery. The completed CRFs at the district and provincial hospitals were sent to the provincial MCH unit together with a monthly report. Maternal deaths were investigated by the heads of district or provincial MCH divisions using the pre-designed investigation form.

Statistical analysis

The sample size of 1,100 pregnant women was calculated from the SMO rate of 2.3% estimated from the medical records of 6,643 total deliveries in the maternity services of Sayaboury Province in 2009 with a precision of 40% of the estimate and 95% confidence interval.

Descriptive statistics, such as means and standard deviations for continuous variables, and proportion for categorical variables, were used to describe baseline characteristics. The maternal complications, maternal near-misses (MNM), maternal deaths (MDs) and severe maternal outcomes (SMOs) were estimated using proportions and their 95% confidence intervals (CIs). The analysis was performed using SPSS version 17.

Ethical approval and participant informed consent

The study was approved by the declaration of personnel and organization department, Ministry of Health (MOH) of Lao PDR. N° 253 on 5 February 2011, declaration of Sayaboury provincial health office [PHO] N° 290, and Khon Kaen University Ethics Committee for Human Research (HE542067). This research is part of PhD study on maternal near-miss and maternal mortality ratio in Sayaboury Province, Lao PDR. All participants were written informed consent for participation in the study. Pregnant women under 18 years old were signed informed consent by their parent.

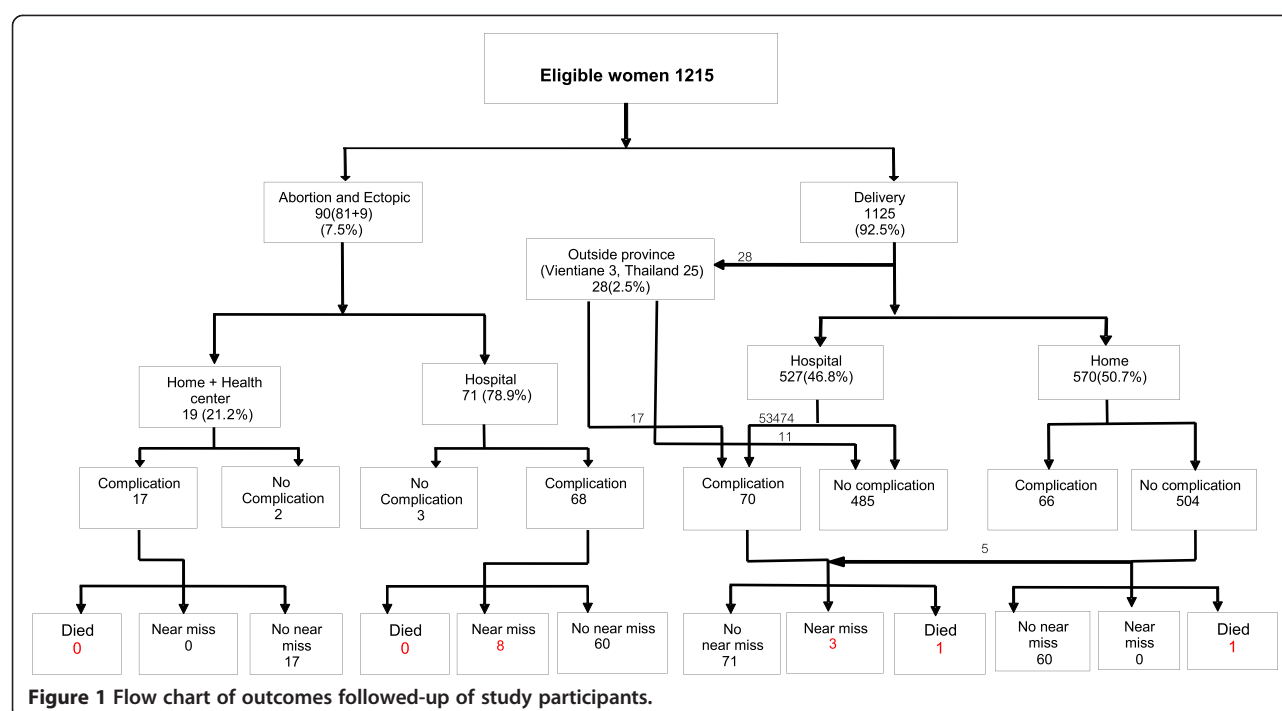
Results

During the study period, 1215 eligible pregnant women were recruited and followed up until 42 days after delivery or termination of pregnancy in the four randomly selected districts of Sayaboury Province, Lao PDR. There were 81 cases of abortion, 9 cases of ectopic pregnancy (7.5%), and 1125 deliveries (92.5%). Five hundred and fifty-five women (49.3%) were delivered in the hospitals, with 527 of these deliveries (46.8%; 527/1125) occurring in the hospitals in Sayaboury Province and 28 (2.5%; 28/1125) in hospitals outside the province (Vientiane and Thailand). Complications were identified in 221 women of whom 68 occurred before 22 weeks of gestation. Among the 221 women, eleven were MNMs and two were maternal deaths. Eight from the eleven MNMs occurred before 22 weeks of gestation (Figure 1).

Table 2 summarizes the baseline characteristics of the 1215 recruited pregnant women. About one-third of the women (38.7%) lived in Sayaboury District. The mean age was 24.4 years (SD 5.6 years) with 11.5% under 19 years of age. Their mean height was 153.4 cm (SD 5.7 cm) and mean weight was 53.0 kg (SD 7.0 kg). The large majority (78%) described themselves as Buddhists. Nine percent had no formal education, and only 2.5% were educated higher than high school level. Most of the women (56.7%) worked as farmers or laborers. Forty three percent of these women were primiparous. 54.5% were institutional deliveries while 43.2% were home deliveries. The largest ethnic group were Lao (70.6%) and 18.3% were from hill tribes (Kamou, Mong, Mien and Pray).

Pregnancy outcomes

Nine hundred and twenty of the recruited women (75.7%) delivered at term (37–42 weeks of gestational age). Preterm deliveries (22–36 weeks of gestational age) occurred in 155 women (12.8%) and post term delivery fifty cases (4%). Abortions and ectopic rupture cases happened in 90 women (7.5%). The great majority of the women (97.2%; 1093/1125) had vaginal deliveries. Only 2.8% had Caesarean sections (Table 3). Among these 1125 deliveries, there were 1121 singletons and four twins giving a



total of 1129 babies. There were 1123 live births (99.8%), six stillbirths (0.5%), 11 early neonatal deaths (1%) and one late neonatal death (0.1%), Table 4.

Maternal complications

The most common complication was haemorrhage in 110 cases (49.7%) and mainly occurred in postpartum period. They were mostly detected in the hospital. Nine of 110 cases were classified as maternal near-miss. The second most common complication was dystocia in 73 cases (33.0%). Forty five cases of them were multiparous and had prolonged labour more than 12 hours. Twenty eight cases were nulliparous with prolonged labour more than 24 hours. All cases of dystocia were assessed by medical doctor in the hospital but the cases detected in the village were confirmed by MCH health center staff. No cases of this category developed MNM or maternal death. The third most common complication was underlying medical conditions (12.6%), including heart diseases, diabetes mellitus, anemia, hyperthyroidism, etc. and one of these led to maternal death. Hypertensive disorder was seen in 16 cases (7.2%); two became maternal near-misses due to pre-eclampsia in the third trimester of pregnancy.

From the eleven near-miss cases 8 were detected at provincial hospital and 3 found at district hospitals, none were detected in the community. There were only two maternal deaths, one caused by pre-eclampsia in the provincial hospital. The other one was cardiopathy died during referring the mother to the hospital. These outcomes are shown in Table 5.

Organ dysfunction system

Nine maternal near miss-cases had multiple organ dysfunctions, and the common organ dysfunctions were respiratory, cardiovascular and renal dysfunctions. A similar pattern of multiple organ dysfunctions was seen in the two maternal deaths (Table 6).

Severe maternal outcomes

There were 13 cases of SMO represent a SMO ratio of 11.6 (95% CI 6.2-19.8)/1,000 live births, and the 11 near-miss cases give a MNM ratio of 9.8 (95% CI 4.9 - 17.5)/1,000 live births). Two maternal deaths represent a maternal mortality ratio (MMR) of 179 (95% CI 50 - 650)/100,000 live births). The mortality index (MI = MD/MNM + MD) was 15.3%, and the maternal near-miss mortality ratio (MNM: MD) was 5.5:1 (Table 7).

Discussion

Our results represent an investigation of maternal mortality and maternal near-miss based on the prospective data collection in both community and local hospitals in the Lao PDR. The presence of organ system dysfunction criteria recommended by the WHO (respiratory, cardiovascular, renal, hepatic, neurologic dysfunctions) were used for the identification of near-miss cases. We found MNM ratio of 9.8 (95% CI: 4.9 -17.5) per 1,000 live births, MMR of 179 (95% CI: 50-650) per 100,000 live birth, both of which appear to be surprisingly low.

For the MMR our finding was quite comparable to the recent study conducted in the North-Western Border of

Table 2 Characteristics of pregnant women in the study (N= 1215)

Characteristics	Number (%)
Districts	
Xienghorn	159 (13.1)
Sayaboury	470 (38.7)
Park lay	347 (28.6)
Kaenthao	239 (19.6)
Age (years)	
< 19	140 (11.5)
19-34	992 (81.7)
≥ 35	83 (6.8)
Mean (±SD)	24.4 (±5.6)
Height (cm)	
< 145	46 (3.7)
145-160	1065 (87.5)
161-170	104 (8.5)
Mean (±SD)	153.4 (±5.7)
Weight (kg)	
cpr< 40	6 (0.5)
40 – 69	1178 (97.0)
≥ 70	31(2.6)
Mean (±SD)	53.0 (±7.0)
Religion	
Buddhist	947 (78)
Catholic	46 (4)
Believer inspirits	222 (18.3)
Education	
Illiteracy	109 (9.0)
Primary school	561 (46.2)
Secondary school	409 (33.6)
High school	106 (8.7)
After high school (others)	30 (2.5)
Occupation	
Farmer/laborer	689 (56.7)
Housewife	401 (33.0)
Government officer/private	125 (10.3)
Parity	
0	525 (43.2)
1-2	441 (36.3)
≥ 3	249 (20.5)
Median (range)	2 (2–3)
Place of delivery	
Provincial hospital	332 (27.3)
District hospital	266 (21.9)
Health center	64 (5.3)

Table 2 Characteristics of pregnant women in the study (N= 1215) (Continued)

Village(home)	525 (43.2)
Other places	28 (2.3)
Ethnic background	
Living in low land area	985 (81.7)
Lao	858 (70.6)
Lue,	73 (6.0)
Gnouan,	47 (3.9)
Thaidam,	5 (0.4)
Other	2 (0.2)
Living in hill tribe area	230 (18.3)
Mong	74 (6.1)
Mien	21 (1.7)
Kamou	115 (9.5)
Pray	20 (1.6)

Thailand where the MMR was 184 (95% CI:150–230) per 100,000 live births [14]. The other comparable result of MMR of 158 per 1,000 live births was reported in the study of maternal mortality estimation at the sub-national level in Bangladesh [15]. Both studies were done in Asian countries similar to Lao PDR.

However, our finding was much lower than those reported in previous studies conducted in other developing countries in other regions. One population based survey of maternal mortality in West Africa found MMR of 311 per 1,000 live births [16]. Another retrospective hospital based study found the MMR of 432 per 1,000 live births in a rural hospital in Sudan [17]. The present study was population based, with prospective data collection in both the community and local hospitals. Retrospective data collection in a central or general hospital (tertiary care) in the previous studies would give higher numbers of maternal death, because of differences in the study population;

Table 3 Pregnancy outcomes

Outcome	Number (%)
Gestational age (weeks)	
< 22 (abortion and Ectopic)	90 (7.4)
22-36	155 (12.8)
37- 42	920 (75.7)
> 42	50 (4.1)
Abortion	81(6.7)
Ectopic rupture	9 (0.7)
Mode of delivery*	
Vaginal delivery	1093 (97.2)*
Caesarean section	32 (2.8)*

*1125 deliveries.

Table 4 Neonatal outcomes

Outcome	Number (%)
Total deliveries	1125 (92.5)
Single deliveries	1121 (99.6)
Twin deliveries	4 (0.4)
Birth weight (grams)	
< 2500	34 (3.0)
2500 – 3000	705 (63.0)
> 3000	380 (34.0)
Mean (±SD)	2956.8 (±359.9)
Live birth	1123 (99.8)
Stillbirth	6 (0.5)
Early neonatal death (<7 days)	11 (1)
Late neonatal death (7 – 28 days)	1 (0.1)

mothers who gave birth in those hospitals came from unlimited catchment areas and higher proportion of complicated cases [16,17].

To some extent, our findings can be explained in the context of the present conditions of MCH and other health services in Sayaboury Province, where the environment was different from the previous studies. Altogether, 629 village health volunteers and 573 traditional birth attendants have been trained in maternal and child care for all villages, and they are regularly supervised and attend refresher training [12]. In addition, the health system has been receiving both technical and financial support from international agencies since 1984 for the MCH services at all levels. Our findings are consistent with the trend in MMR of Lao PDR reported from 1990 to 2010 by WHO, et al. [18]. The estimates MMR per 100,000 live births were 1,600 in 1990 and 470 in 2010 with a 70% reduction between the two years. The trend is progress towards improving maternal health according to the MDG 5 [18].

Although there were difficulties in transferring patients to the provincial hospital during the wet season, the geography of the province is such that all its districts share a border with Thailand and some with Vientiane

Table 5 Frequencies of near misses and maternal deaths by potential threatened conditions

Conditions	Numbers*	Number of near miss (%)	Number of maternal death (%)
Haemorrhage	110	9 (8.2)	0
Hypertensive disorders	16	2 (12.5)	1 (6.3)
Previous medical conditions	28	0	1 (3.6)
Dystocia	73	0	0
Other	2	0	0
Total	221	11 (5.0)	2 (0.9)

*One woman could have more than one conditions.

Table 6 Frequencies of maternal near-miss and maternal death by type of organ systems dysfunction

Dysfunctional organ	Number of near miss cases	Number of maternal death
Respiratory dysfunction	9	2
Renal dysfunction	-	1
Cardiovascular dysfunction	8	2
Hepatic dysfunction	1	-
Neurologic dysfunction	1	1

Province. When an emergency occurs, there were options for seeking care in a neighboring country or in Vientiane Capital City. The above reasons may account for the low maternal mortality found in our study compared to those suggested by the national statistics [4,5] and previous studies in developing countries [11,16,17].

The present study also found a maternal near-miss ratio of only 9.8 per 1,000 live births which was much lower than those in previous studies. Souza et al. reported the MNM ratio of 34.3 per 1,000 live births in the WHO global survey on maternal and perinatal health done in 120 of eight Latin American countries [7]. Almerie et al. reviewed cases of maternal near-miss and maternal mortality in a maternity university hospital, Damascus, in Syria [6] and reported the MNM ratio of 32.9 per 1,000 live births. A prospective study in Ghana showed the MNM ratio of 28.6 per 1000 live births in a teaching Hospital (KBTH) [19]. Ali et al. reported the MNM ratio of 21.1 per 1,000 live births in a rural hospital in Sudan [17]. The reasons for our lower ratio may be because the previous studies were hospital-based and tend to have higher ratios because of the higher proportion of complicated cases than our community-based study. However our result was quite similar to the report of the WHO Multicounty Survey on Maternal and Newborn Health [20] which presented the ratio of 8.3 per 1,000 live births. In addition, it was little higher than that of Jabir et al. reported the ratio of 5.06 per 1,000 live births in Baghdad, Iraq [21].

The rates of maternal near-miss may differ when using different identification criteria. A one year retrospective

Table 7 Maternal near-misses and maternal deaths

Outcomes	Number	Ratio (95% CI)	Rate*** (95% CI)
Severe maternal outcome	13	11.6* (6.2-19.8)	10.7 (6.3 -18.2)
Maternal near- miss	11	9.8* (4.9 – 17.5)	9.1 (5.1- 16.2)
Maternal death	2	178.7** (50 – 650)	
Mortality index		15.3%	
Maternal near-miss mortality ratio (MNM: 1 MD)		5.5: 1	

*per 1000 live births, **per 100,000 live births, ***per 1000 eligible women.

chart review study of medical records of 1,163 obstetric hospital admissions of a tertiary maternity hospital in Rio de Janeiro, Brazil was conducted in 2013 [22]. It underlined that different approaches entail different estimates of MNM. The maternal near-miss ratio was 27 per 1,000 live births using WHO maternal near-miss criteria compared with 123 per 1,000 live births of using the Waterston criteria. Furthermore a systematic review of the prevalence of maternal near miss by Tunçalp, et al. [23] reported the rates of maternal near-miss varied between 0.04% and 4.54% for management-based criteria and between 0.14% and 0.92% for organ-based dysfunction based criteria. The prevalence using different criteria were higher in low-income and middle-income countries of Latin America and Africa [22,23].

Our finding of maternal near-miss detected may be underestimated. There are several possible reasons for this. Firstly, maternal near-miss was a new marker of health and obstetric care in our setting. The local co-coordinators (VHV, TBA, MCH health center staff) might have difficulties in understanding the concept and process of MNM identification and led to miss some MNM in the communities. Secondly, limitation of the MCH staff and facilities at the district hospitals might be the important factors that did not allow investigators to apply full WHO criteria to detect a maternal near-miss. This was due to a number of factors: (a) the laboratories at the district hospitals had a limited capacity to confirm near-miss cases; (b) the supply of donated blood was inadequate; in the four study hospitals only the provincial hospital had a blood bank, although two district hospitals did have blood stores; and (c) there was a lack of medical equipment and alternative facilities for the care of severely ill patients at the district hospitals. Only the provincial hospital had an intensive care unit. As a consequence, some cases were probably not classified as near-misses because the severity of their condition was unable to be confirmed by the existing facilities.

One significant finding in this study is the very high proportion (7 from 11) of MNMs occurred early in pregnancy, 2 cases related to abortion complication and 5 caused of ectopic pregnancy. Maternal and child health care providers and policy makers should be informed about this important cause of MNM.

They were 9% (8/90 abortions) of all abortion and ectopic pregnancies. This figure was lower than that of 11.1% (61/549 abortions) found in a surveillance network study to identify severe maternal complications associated with abortion in 27 referral obstetrics units across regions of Brazil [24].

Requirement of the complexity of care could be estimated from the MNM incidence and SMO ratio. The higher values, the greater the extent to which women require high complexity care. Our findings show the

mortality index (MI) was 15% compared to 8.5% of Cecatti et al. who evaluated maternal near miss using WHO criteria and maternal death related to organ failure in Brazil [25]. van den Akker et al. reported a MI of 12% in their study evaluating maternal near miss using organ-failure based criteria as a tool in Southern Malawi [26]. The mortality index (MI) represents an estimate of performance. It is recommended that an institute with high index (>20%) may have inadequate quality of obstetric care for the severe cases [24]. Although we had small maternal index in our setting, we could not be sure that there is adequate quality of obstetric care for the severe cases in Sayabury Province. There is lack of resources for obstetric care, such as blood bank, operation room, etc. in many district hospitals of the province. The maternal near-miss: mortality ratio (MNM: 1 MD) was 5.5:1. The ratio can provide direct information on problems related to care of severity obstetric complication and could be used as marker of obstetric care [24].

Strength of the study

This was the first population-based descriptive study involving a follow-up of pregnant women since the date of their last menstrual period until within 42 days after termination of pregnancy in order to identifying the incidence of MNM and MD in both the community and local hospitals in Lao PDR. The WHO clinical criteria of organ systems dysfunction were used for the identification of near-miss cases, allowing potential international comparisons. Its main strengths were the use of trained PHC workers (TBAs and VHVs) and health center staff to regularly screen eligible pregnant women in the villages and carry out the follow-up of complication cases to detect maternal near-misses and record maternal mortality. The early detection of maternal complication cases in the community and their referral to hospitals for prompt treatment were used to the maximum possible extent to reduce the number of maternal deaths. The follow-up model used in our study is expected to have implications, which will be benefit to women in developing countries.

Limitations

The study was designed to identify near-misses and maternal deaths in both the community and the local hospitals. However, the WHO standard criteria for the identification of maternal near-misses could not be used in the community, TBAs in the village and local coordinator at the health centers might have limited knowledge to confirm MNMs. In addition, the district hospitals had limited resources for assessing organ dysfunctions, such as limited supply of blood and laboratory facilities. These factors might cause an underestimation of near-miss rates. The maternal near-misses could have been underestimated by the application of the WHO definition of a near-miss which

relies on good laboratory and management-based criteria. These potential limitations are consistent with those presented in study of Cecatti et al. [25]. van den Akker et al. used WHO MNM approach studied at Malawi [26] and the study of Nelissen et al. by applying WHO maternal near-miss criteria in low resources setting in rural hospital Tansania [27].

Implications

The future development of maternal health services (MHS) should include an upgrading of the capacities of MCH services in local hospitals and ways of improving these services in local health centers so that local MHS staff and midwives are better able to recognize and respond to the important factors associated with SMOs. This study was, in essence, a pilot project for the detection of maternal near-misses and maternal deaths in Lao PDR. Using the lessons learnt from this study, it is proposed that the Lao Ministry of Health should consider a nation-wide study of maternal near-misses, for the future development of maternal health services and also for further health research on MCH data collection in poorly resourced areas, especially in the remote provinces of Lao PDR.

Conclusion

The study shows a surprisingly low MNR and MMR. This may raise questions about the usefulness of the WHO definition of a near-miss in settings with low resources. However, adapted near-miss criteria for the low resources situation may be benefit to the implications for the developing world where health services are also poorly resourced.

Competing interests

The authors declare that they have no competing interest.

Authors' contributions

LP is the first author, responsible for conceptualization, study design, conducted data collection, data analysis, interpretation and prepared manuscript. ML is academic main advisor, supported in conceptualization, study design, conducted data collection, data analysis, interpretation and manuscript reading and revisions. PL and MHB are co-advisors, participated in support on conceptualization, study design and manuscript reading and revisions. All authors read and approved the final manuscript.

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CLINICAL ARTICLE

Cesarean rates and severe maternal and neonatal outcomes according to the Robson 10-Group Classification System in Khon Kaen Province, Thailand

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Keywords: 10-Group Classification System; Cesarean; Robson classification; Severe maternal morbidity; Severe neonatal morbidity

Synopsis: The overall rate of cesarean was high; three of four procedures were performed for women in Robson groups 5, 1, and 2.

Abstract

Objective: To assess cesarean rates and maternal and neonatal outcomes in each group in the Robson 10-Group Classification System (TGCS).

Methods: In a cross-sectional study, data were reviewed from all pregnant women who delivered at 24 government hospitals in Khon Kaen Province, Thailand, in 2014. Delivery and perinatal outcomes were recorded.

Results: Of 18 043 deliveries, 5666 (31.4%) were by cesarean. Women in group 5 (previous cesarean) accounted for the most cesareans (1472, 26.0%). Groups 1 and 2 (nulliparous women) accounted for 2355 (41.6%) of procedures; the rate of cesarean within these two groups was 19.4% (1162/5981) and 71.2% (1193/1675), respectively. As compared with group 1, women in groups 2, 4, 6, 7, and 10 had significantly increased risk of severe maternal outcomes, and those in groups 6, 7, 8, 9, and 10 had an increased risk of severe neonatal outcomes.

Conclusion: The rate of cesarean in the study setting was high, and three out of four procedures were performed for women in groups 5, 1, and 2. Interventions should be focused on these groups to reduce the overall cesarean rates.

1 INTRODUCTION

In 1985, WHO stated that there was no justification for any region to have cesarean rates higher than 10%–15% because there was no evidence that maternal and neonatal outcomes are better when the cesarean rate is above this range [1]. Since then, the recommended rate of 10%–15% has been internationally accepted as a standard threshold. The global rate of cesarean has been estimated to be approximately 19% on the basis of recent nationally representative data from 150 countries [2]. Nevertheless, the rate varies widely among geographic regions. The average rate of cesarean is highest in Latin America and the Caribbean (40.5%), followed by North America (32.3%), Oceania (31.1%), Europe (25%), Asia (19.2%), and Africa (7.3%) [2].

High rates of cesarean adversely impact healthcare expenditure. Among countries with rates above 15%, it is estimated that a reduction to 15% would lead to a global saving of approximately US\$2.32 billion [3]. By contrast, among countries with cesarean rates below 10%, the cost of achieving a rate of 10% is estimated to be approximately \$432 million [3].

Many studies have demonstrated that cesarean increases the risks of serious maternal and neonatal outcomes such as postpartum hemorrhage, injury to urinary tract, neonatal respiratory morbidity, abnormal placentation, and uterine rupture in future pregnancies [4–7]. Therefore, cesarean should be performed only when medically necessary [7,8].

The Robson 10-Group Classification System (TGCS) has been proposed to categorize pregnant women admitted for delivery into 10 clinically relevant groups, thereby facilitating an assessment of the cesarean rate in each group [9]. The TGCS classifies women by using six basic obstetric characteristics: parity, onset of labor, number of fetuses, fetal presentation and lie, previous cesarean, and pregnancy length at delivery (Figure 1). The TGCS facilitates a standardized assessment of cesarean rates and pregnancy outcomes within and across these 10 groups, both within the same facility and among facilities [8,9].

The TGCS was proposed as the most appropriate system for current international and local needs [10]. In 2014, a systematic review [11] reported that the main strengths of the TGCS were its simplicity, reproducibility, robustness, reliability, and flexibility, thus making it easy to implement and interpret. In 2015, WHO proposed the TGCS as a global standard for assessing and monitoring cesarean at healthcare facilities [8,12]. The advantage of using the TGCS for analyzing overall cesarean rates in detail is well documented [9,11]; however, the TGCS can also validate the quality of the data [13]. Simple assessments, such as how the numbers add up and in particular the relative sizes of the individual groups, can provide much information. This is partly because the percentages of women with breech presentation, twins, and transverse lie are highly consistent, and in other groups the cesarean rate is always either 100% (group 9) or 1%–3% (group 3). In many datasets, however, there are a few women who are not classifiable, and the percentage of these women reflects the validity and quality of the data collection in that particular organization. There are potential limitations in implementing the TGCS, mainly related to the availability and validity of the information on onset of labor and pregnancy length at

delivery. This might lead to the misclassification of some women in the 10 groups. Moreover, the TGCS itself is not an intervention to reduce unnecessary cesarean procedures, but rather a monitoring tool to identify where the problems are so that appropriate interventions can be implemented.

The national rate of cesarean delivery in Thailand is 34.1%, which suggests that some procedures that are performed are not medically necessary [7]. The aim of the present study was to use the TGCS to assess the overall rate, Robson group-specific rates, and relative contribution of each Robson group to the overall rate of cesarean, and to determine the risk of severe maternal and neonatal adverse outcomes for each TGCS group in Khon Kaen Province, Thailand.

2 MATERIALS AND METHODS

In the present cross-sectional study, data were reviewed from all pregnant women who delivered at government hospitals in Khon Kaen, Thailand, between January 1 and December 31, 2014. The study was approved by the Ethics Committees of Khon Kaen University and Khon Kaen Hospital. Patient informed consent was waived because it was a retrospective medical record review.

Khon Kaen is the second largest province in northeast Thailand, with a population of about 1.8 million and approximately 18 000 deliveries per annum. There are three tertiary hospitals and 21 community hospitals. Among the 21 community hospitals, cesareans can be performed at only seven. For the present study, the delivery records of the 24 hospitals were reviewed. Women who delivered in private

hospitals, and women whose medical records were not available were excluded from the study.

Medical records (both maternal and neonatal) for the women identified through the delivery summary records were reviewed until discharge. There was no limit to the number of days reviewed after delivery. Trained research assistants extracted maternal baseline characteristics, variables for the TGCS, final mode of delivery, and maternal and neonatal outcomes. Maternal baseline characteristics included age, pre-pregnancy body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters), education, occupation, and underlying medical conditions. Variables for the TGCS included parity, number of fetuses, fetal presentation and lie, pregnancy length at delivery, previous cesarean, and type of labor onset (Figure 1). Maternal outcomes included estimated blood loss, sepsis, peripartum hysterectomy, admission to intensive care unit, and maternal death. Neonatal outcomes included Apgar score at 5 minutes, requirement for respiratory support, cardiopulmonary resuscitation, admission to neonatal intensive care unit, intrapartum fetal death (fresh stillbirth), and early neonatal death.

Statistical analyses were performed using STATA version 10 (StataCorp, College Station, TX, USA). Maternal and neonatal outcomes were calculated for each Robson group. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to compare maternal and fetal outcomes between each Robson group, using group 1 as the reference. The model was adjusted for maternal age, maternal BMI, education, and occupation. $P < 0.05$ was considered statistically significant.

3 RESULTS

In 2014, there were 19 087 deliveries in Khon Kaen Province. Of these, 751 (3.9%) took place in private hospitals and were excluded because medical record reviews were not allowed. Additionally, medical records were not available for 199 (1.1%) deliveries in government hospitals. Overall, 18 137 medical records were reviewed; of these, information for TGCS was not completely available for 94 (0.5%) deliveries and these were excluded from the analysis. Therefore, 18 043 deliveries were included (Figure 2).

The rate of cesarean was 31.4% (5666/18 043) overall, and 44.1% (4388/9949), 21.2% (1254/5913), and 1.3% (29/2181) in tertiary, large, and small community hospitals, respectively.

Table 1 presents the distribution of women and cesarean procedures in all government hospitals in Khon Kaen province stratified by the TGCS. Approximately two-thirds of women were classified into groups 1 and 3; groups 2 and 5 accounted for 17.5% of the population.

Women with abnormal fetal lie (group 9), previous cesarean (group 5), and breech presentation (groups 6 and 7) had the highest cesarean rates, followed by group 2 and those with multiple pregnancies (group 8). The lowest rate of cesarean was observed in group 3. Overall, group 5 made the greatest contribution to the overall cesarean rate with an absolute and relative contribution of 8.2% and 26.0%, respectively. The relative contribution of groups 1 and 2 to the cesarean rate was 20.5% and 21.1%, respectively.

As compared with group 1, women in groups 2, 4, 6, 7, and 10 had significantly increased risks of severe maternal adverse outcomes after adjustment for maternal age, BMI, education, and occupation (Table 2). There were four maternal deaths: two in group 4, and one each in groups 2 and 10.

Women in group 3 had the lowest rate of severe neonatal adverse outcomes at 4.3%, which was significantly lower than group 1 (Table 3). However, women in groups 6, 7, 8, 9, and 10 had a significantly increased risk of severe neonatal outcomes after adjustment for maternal age, BMI, education, and occupation (Table 3).

4 DISCUSSION

The overall cesarean rate in the present study was 31.4%, but varied from 44.1% in tertiary hospitals to 1.3% in small community hospitals. The major contributions to this high rate were from TGCS groups 1, 2, and 5. Women in TGCS group 6, 7, and 10 had significantly increased risks of both severe maternal and neonatal outcomes.

The high rate of cesarean found in the present study was mainly due to women in group 5 and groups 1 and 2. Studies in Latin America and Egypt also found that group 5 (previous cesarean) made the greatest contribution to the overall rate of cesarean (26.7% [14] and ~30% [15], respectively). Indeed, the major contribution of previous cesarean to the overall rate has been consistently confirmed in studies from Singapore, Brazil, Lithuania, and Italy, with a relative contribution ranging from 15.4% to 67.7% [16–19]. Given the high rate of cesarean in the present population,

the size of group 5 (8.2%) might seem smaller than expected, which in turn might raise concerns about the possibility of misclassification, particularly between group 5 and groups 2 and 4. The relatively small size of group 5 in the present study might also be secondary to the high number of nulliparous women (groups 1 and 2), who accounted for approximately 42.5% of the study population.

Almost all women with a previous cesarean have a repeat procedure in Khon Kaen (unpublished data). To reduce the frequency of repeat cesarean, vaginal birth after cesarean should be considered, particularly for women with one previous transverse low-segment scar [20]. If the rate of cesarean in group 5 could be reduced to 60%, the overall rate would be reduced approximately 3 percentage points from 31.4% to 28.1%.

As previously reported in other facilities worldwide, there is a trend of high rates of cesarean in groups 1 and 2 [16–19,21]. The contribution of these women to the overall rate in the present study was 41.6%. The 20% rate of cesarean observed in group 1 might be considered unjustified; it has been proposed that the rate in this group should be approximately 10% or below [13,22]. The excessively high cesarean rates among women in groups 1 and 2 are probably associated with increased use of cesarean without medical indication and inappropriate induction of labor [21].

Many women and perhaps some obstetricians are unaware of the immediate and long-term adverse consequences of cesarean. Many women are scared about labor pain and decide to have a pre-labor procedure. In terms of time management, it is more convenient for both women and obstetricians to choose cesarean rather than

vaginal delivery. Additionally, some obstetricians chose to recommend pre-labor cesarean to avoid unexpected complications during labor and delivery, and possible medical lawsuits. Importantly, the relative sizes of groups 1 and 2 can be an important source of information. They reflect the proportion of women who go into spontaneous labor as opposed to planned delivery by induction or prelabor cesarean. The ratio should be interpreted in relation to the frequency of stillbirths in the two groups. In the present population, the ratio was 3.6, which is similar to that in the “reference” population of the WHO Multi-country Study [22]. Alternatively, this ratio could miss the potential misclassification of women who were classified as “induced” (group 2) who actually received oxytocin only to augment labor (group 1) [13]. Misclassification has been suggested as an important reason for ratios lower than 2:1. The present findings indicate the need for a meticulous assessment of the indications for performing cesarean and use of oxytocin in groups 1 and 2, which are generally low risk for cesarean, and indications for induction in group 2. Importantly, limiting the number of cesareans among nulliparous women is the key to lowering the trend toward increased cesarean; if it can be done successfully, it will also reduce the numbers of women in group 5, which will further simultaneously reduce the contribution of group 5 to the overall rate of cesarean. If the cesarean rate in group 1 could be lowered from 20% to 10%, the overall rate would be reduced by approximately 3 percentage points.

In a study at Singapore General Hospital, approximately 90% of women with multiple pregnancies (group 8) underwent cesarean [16]. Similarly, most women in group 8 underwent cesarean in the present study (a rate of approximately 70%). Two studies have reported that perinatal morbidities among term twin pregnancies with leading

cephalic presentation are similar for women who deliver vaginally and those who deliver by cesarean [23,24]. Moreover, a randomized controlled trial from the Twin Birth Study comparing the safety of planned cesarean versus vaginal delivery among uncomplicated pregnancies at 32–38 weeks with leading cephalic presentation [25] showed that there was no significant difference in either mortality rate or neurodevelopmental delay in offspring at 2 years of age. On the basis of these findings, an institutional policy for promoting vaginal delivery among uncomplicated twin pregnancies in which the first twin is in cephalic presentation should be implemented. The rates of cesarean for breech presentation, transverse lie, and multiple pregnancies (groups 6–9) are typically high, but these groups represented only 4.2% of the obstetric population in Khon Kaen. Interventions to reduce the overall rate of cesarean that focus on these groups could have little value.

The present study has demonstrated the ease of implementing the WHO-recommended TGCS in all hospitals in Khon Kaen Province, including small community hospitals. The routinely collected information, including onset of labor, recorded in medical records allowed the classification of more than 99% of women according to the TGCS. In the study setting, differentiation between the types of onset of labor is made explicitly in the medical record, minimizing the misclassification that often rises around this variable. There is a specific item for recording the time of the onset of labor in the delivery summary for spontaneous labor. If labor is induced, or in the case of elective cesarean, this fact is recorded rather than the time of onset of labor. The required information was readily extracted from medical records by a research assistant with minimal training. In short, the present study did not find any barriers in implementing the TGCS.

The strengths of the study include the large study sample size covering all deliveries in government hospitals in Khon Kaen Province. Additionally, meetings with the research assistants were organized to explain the data collection process and the definition of variables across all included facilities. Furthermore, the study collected data regarding severe maternal and neonatal morbidity and mortality stratified by the TGCS—factors that are rarely reported in the literature—thereby enabling the cesarean rate and severe adverse pregnancy outcomes to be comprehensively compared with data from other healthcare facilities.

The study has some limitations. First, data were collected for only a 1-year period; thus, it was not possible to determine trends in cesarean or adverse perinatal outcomes in each group. Assessing cesarean rates and outcomes over time is a strength of the TGCS and would facilitate the identification of cesarean rates associated with optimal outcomes in each group. Second, data from private hospitals were not included. There were only 751 (3.9%) deliveries in these private hospitals during the study period; thus, the lack of information from private hospitals is unlikely to have a significant effect on the main findings presented, although the rates of cesarean in the private sector are expected to be higher.

In conclusion, the rate of cesarean in Khon Kaen, Thailand, was found to be high, and most procedures were performed for women in groups 5, 1, and 2. Interventions to reduce the incidence of cesarean specifically among women in these groups would help to reduce the overall rate of cesarean.

Author contributions

NK and PL developed the research question and the research proposal, with input from APB and MR. NK, CK, and US collected and analyzed the data. NK, PL, and CK drafted and revised the manuscript. US, APB, and MR reviewed the manuscript critically. All authors approved the final version of the manuscript.

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Conflicts of interest

The authors have no conflicts of interest.

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Figure legends

Figure 1 Robson 10-Group Classification System. Reproduced from WHO Statement on Caesarean Section Rates [8], by permission of the World Health Organization.

Figure 2 The study population.

Table 1 Distribution of all cesarean procedures stratified by the Robson 10-Group Classification System.

Group	Number of cesareans/total number of deliveries (overall: 5666/18 043)	Size of group, % ^a	Cesarean delivery rate in group, %	Contribution of cesareans in group to total number of deliveries, % (overall: 31.4) ^a	Relative contribution to overall rate, % (overall: 100) ^a
1	1162/5981	33.1 (5981/18 043)	19.4	6.4 (1162/18 043)	20.5 (1162/5666)
2	1193/1675	9.3 (1675/18 043)	71.2	6.6 (1193/18 043)	21.1 (1193/5666)
3	478/5908	32.7 (5908/18 043)	8.1	2.6 (478/18 043)	8.4 (478/5666)
4	405/816	4.5 (816/18 043)	49.6	2.2 (405/18 043)	7.1 (405/5666)
5	1472/1481	8.2 (1481/18 043)	99.4	8.2 (1472/18 043)	26.0 (1472/5666)
6	280/298	1.7 (298/18 043)	94.0	1.6 (280/18 043)	4.9 (280/5666)
7	252/271	1.5 (271/18 043)	93.0	1.4 (252/18 043)	4.4 (252/5666)
8	95/139	0.8 (139/18 043)	68.4	0.5 (95/18 043)	1.7 (95/5666)
9	38/38	0.2 (38/18 043)	100	0.2 (38/18 043)	0.7 (38/5666)
10	291/1436	8.0 (1436/18 043)	20.3	1.6 (291/18 043)	5.1 (291/5666)

^a Numbers used to calculate percentages are given in parentheses.

Table 2 Severe maternal outcomes stratified by the Robson 10-Group Classification System.

Group	Severe maternal outcomes ^a	Unadjusted OR (95% CI)	Adjusted OR (95% CI) ^b
1	12/5018 (0.2)	Ref.	Ref.
2	11/1384 (0.8)	3.3 (1.5–7.6)	2.7 (1.2–6.2)
3	16/5292 (0.3)	1.3 (0.60–2.7)	0.8 (0.4–1.7)
4	15/742 (2.0)	8.6 (4.0–18.5)	4.6 (2.1–10.4)
5	7/1197 (0.6)	2.5 (1.0–6.3)	1.5 (0.6–3.8)
6	3/222 (1.4)	5.7 (1.6–20.4)	4.6 (1.3–16.7)
7	6/218 (2.8)	11.8 (4.4–31.8)	5.5 (1.9–15.5)
8	0/109	–	–
9	1/30 (3.3)	14.4 (1.8–114.3)	7.9 (1.0–64.6)
10	24/1218 (2.0)	8.4 (4.2–16.8)	6.2 (3.1–12.7)

Abbreviation: OR, odds ratio; CI, confidence interval.

^a Including at least one of the following: severe postpartum hemorrhage, sepsis, peripartum hysterectomy, maternal admission to intensive care, maternal death. Values are given as number/total number (percentage).

^b Adjusted for age, body mass index, education, and occupation.

Table 3 Severe neonatal outcomes stratified by the Robson 10-Group Classification System.

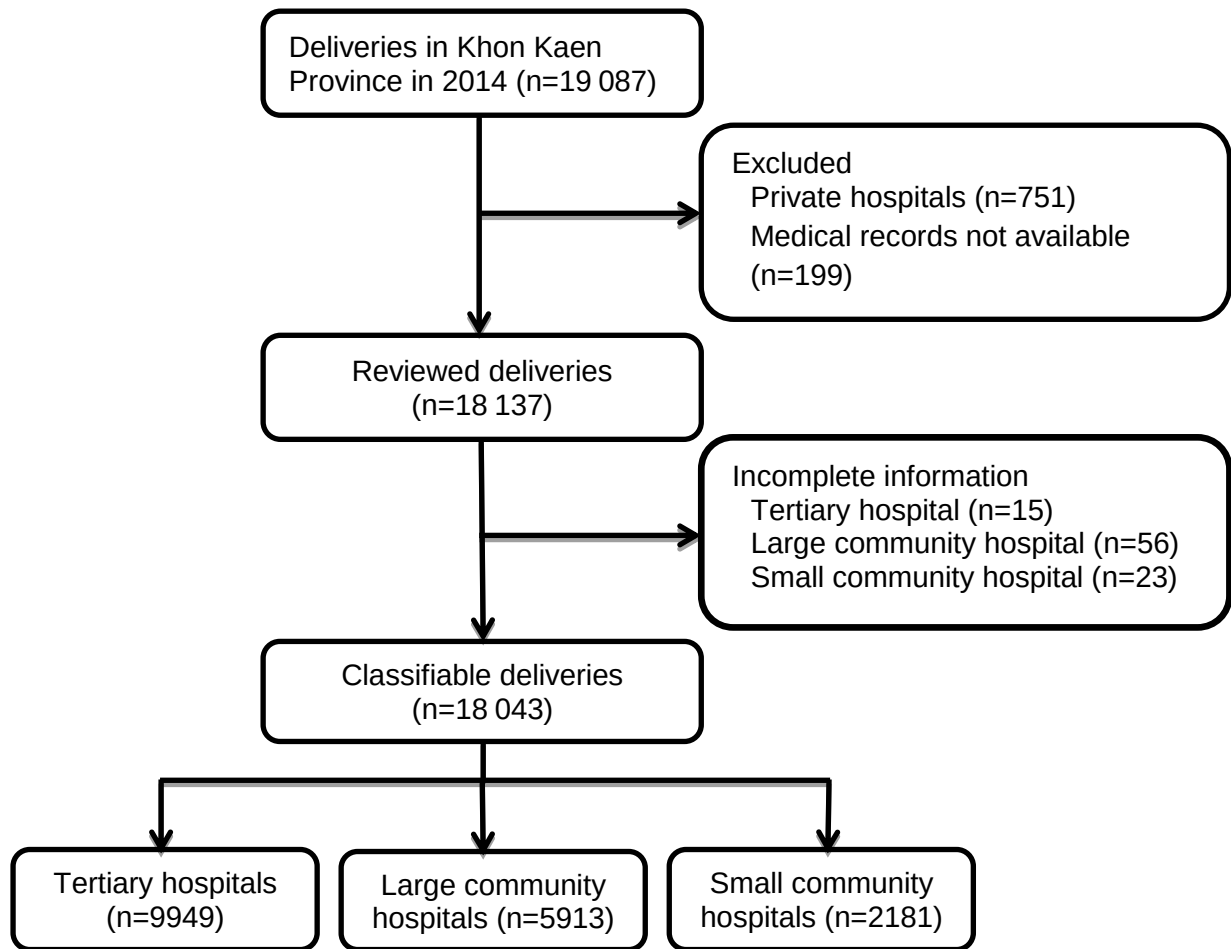
Group	Severe neonatal outcomes ^a	Unadjusted OR (95% CI)	Adjusted OR (95% CI) ^b
1	355/5016 (7.1)	Ref.	
2	129/1385 (9.3)	1.4 (1.1–1.7)	1.1 (0.9–1.4)
3	229/5299 (4.3)	0.6 (0.5–0.7)	0.5 (0.4–0.6)
4	65/733 (8.9)	1.3 (1.07–1.7)	1.0 (0.8–1.4)
5	110/1197 (9.2)	1.3 (1.1–1.7)	1.0 (0.8–1.3)
6	61/221 (27.6)	5.0 (3.7–6.9)	4.3 (3.1–6.0)
7	58/219 (26.5)	4.7 (3.4–6.5)	3.7 (2.6–5.2)
8	62/108 (57.4)	17.7 (11.9–26.3)	15.6 (10.4–23.2)
9	9/30 (30.0)	5.6 (2.6–12.4)	4.8 (2.2–10.8)
10	304/1218 (25.0)	4.4 (3.7–5.2)	4.2 (3.5–5.0)

Abbreviations: OR, odds ratio; CI, confidence interval.

^a Including at least one of the following: Apgar score at 5 min <7, endotracheal tube, continuous positive airway pressure, respirator, cardiopulmonary resuscitation, admission to neonatal intensive care unit, intrapartum death, stillbirth, early neonatal death (<7 d). Values are given as number/total number (percentage).

^b Adjusted for age, body mass index, education, and occupation.





RESEARCH

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Management of pregnancy at and beyond 41 completed weeks of gestation in low-risk women: a secondary analysis of two WHO multi-country surveys on maternal and newborn health

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Abstract

Background: The World Health Organization (WHO) recommends induction of labour (IOL) for women who have reached 41 completed weeks of pregnancy without spontaneous onset of labour. Many women with prolonged pregnancy and/or their clinicians elect not to induce, and chose either elective caesarean section (ECS) or expectant management (EM). This study intended to assess pregnancy outcomes of IOL, ECS and EM at and beyond 41 completed weeks.

Methods: This study is a secondary analysis of the WHO Global Survey (WHOGS) and the WHO Multi-country Survey (WHOMCS) conducted in Africa, Asia, Latin America and the Middle East. There were 33,003 women with low risk singleton pregnancies at ≥ 41 completed weeks from 292 facilities in 21 countries. Multilevel logistic regression model was used to assess associations of different management groups with each pregnancy outcome accounted for hierarchical survey design. The results were presented by adjusted odds ratios (aORs) with 95% confidence intervals (CIs) after adjusting for age, education, marital status, parity, previous caesarean section (CS), birth weight, and facility capacity index score.

Results: The prevalence of prolonged pregnancy at facility setting in WHOGS, WHOMCS and combined databases were 7.9%, 7.5% and 7.7% respectively. Regarding to maternal adverse outcomes, EM was significantly associated with decreased risk of CS rate consistently in both databases i.e. (aOR0.76; 95% CI: 0.66–0.87) in WHOGS, (aOR0.67; 95% CI: 0.59–0.76) in WHOMCS and (aOR0.70; 95% CI: 0.64–0.77) in combined database, compared to IOL. Regarding the adverse perinatal outcomes, ECS was significantly associated with increased risks of neonatal intensive care unit admission (aOR1.76; 95% CI: 1.28–2.42) in WHOMCS and (aOR1.51; 95% CI: 1.19–1.92) in combined database compared to IOL but not significant in WHOGS database.

(Continued on next page)

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Conclusions: Compared to IOL, ECS significantly increased risk of NICU admission while EM was significantly associated with decreased risk of CS. ECS should not be recommended for women at 41 completed weeks of pregnancy. However, the choice between IOL and EM should be cautiously considered since the available evidences are still quite limited.

Keywords: Prolonged pregnancy, Post-term pregnancy, Induction of labour, Elective caesarean section, Expectant management, Pregnancy outcomes

Plain English summary

Pregnancies beyond 41 completed weeks are associated with adverse outcomes. Hence, the World Health Organization recommends inducing labour for women who have reached 41 completed weeks of pregnancy without spontaneous labour pain. Many of such women and/or their clinicians do not want to induce, instead they prefer to deliver by caesarean section or expectant management (awaiting spontaneous onset of labour).

We compared pregnancy outcomes of women at 41 completed weeks of pregnancy by three different managements – induction of labour, elective caesarean section and expectant management using two large, WHO databases conducted in Africa, Asia, Latin America and the Middle East. We did not find any difference in adverse pregnancy outcomes between induction group and expectant group except higher caesarean section rate in induction of labour group.

We found that neonatal intensive care unit admission was higher in newborns delivered by elective caesarean section compared to that of induction of labour. Our findings showed that elective caesarean section had increased risk of adverse neonatal outcomes and should not be recommended. However, the choice between induction of labour and expectant management should be cautiously considered since the available evidences are still quite limited.

Background

The World Health Organization (WHO) recommends induction of labour (IOL) for women who have reached 41 completed weeks of pregnancy without spontaneous onset of labour [1]. Rates of IOL vary across countries. IOL rates for high-income countries were 23.4% of deliveries in United States in 2010 [2], 22.1% of deliveries in England between 2011 and 2012 [3] and 25.4% of deliveries in Australia in 2010 [4]. The rates also vary for low and middle-income countries (LMIC). The WHO Global Survey on Maternal and Perinatal Health reported the prevalence of IOL in facility deliveries as 4.4% in seven African countries, 12.1% in nine Asian countries [5] and 11.4% in eight Latin American countries [6]. IOL is specifically recommended to prevent complications of prolonged pregnancy, such as increased perinatal mortality,

stillbirth, fetal growth restriction, meconium aspiration syndrome and macrosomia [7–10]. However, IOL itself carries the risk of uterine hyperstimulation, increased instrumental delivery, uterine rupture, fetal distress and Caesarean section (CS) [1].

Many women with prolonged pregnancy (≥ 41 weeks) and/or their clinicians often elect not to induce, and chose either ECS or expectant management EM (awaiting spontaneous onset of labour). The reasons for choosing CS may be not only to manage the prolonged pregnancy, but also be the preferred mode of delivery for the women and/or the clinicians [11].

Systematic reviews of randomized controlled trials have compared the risks and benefits of IOL compared to EM at and beyond 41 weeks gestation [12–16]. All these systematic reviews assessed perinatal death and CS rate as primary outcomes, and other maternal and perinatal morbidities such as postpartum haemorrhage, ruptured uterus, meconium aspiration, Apgar score, NICU admission, stillbirth and early neonatal death as secondary outcomes. These reviews consistently reported that IOL at 41 completed weeks of gestation reduced the complications of postterm pregnancies compared to EM. However, the risks and benefits of IOL compared to ECS for women with prolonged pregnancy have not been as thoroughly explored. Furthermore, analysis of clinical data can provide insight into the effectiveness of interventions in “real life” settings. This analysis aimed to explore not only the risks and benefits of IOL but also that of ECS regarding to pregnancy outcomes among women with prolonged pregnancy in two large multi-country databases of facility deliveries in predominantly low- and middle-income countries.

Methods

Study design and setting

This study is a secondary analysis of two WHO databases: the WHO Global Survey (WHOGS) on Maternal and Perinatal Health [17] conducted in Africa, Asia and Latin America and the WHO Multi-country Survey (WHOMCS) on Maternal and Newborn Health conducted in Africa, Asia, Latin America and the Middle East [18]. WHOGS was conducted to explore the

association between CS and maternal and perinatal outcomes in 286,565 women giving birth in 373 facilities in 24 countries during 2004–2008. Building on the existing WHOOGS network, the WHOMCS aimed to assess severe maternal and perinatal morbidity using the WHO maternal near-miss criteria in 314,623 women at 359 facilities in 29 countries during 2010–2011. All the participating countries except Japan and Qatar were in low and middle-income category (according to World Bank classifications) [19].

Details of the survey methods have been published elsewhere [17–20]. In brief, they were multi-centre, facility based, cross-sectional studies which used a stratified multistage cluster sampling method to select a sample of countries, provinces and health facilities. For the WHOOGS, fourteen sub-regions from the six WHO regions were identified as the sampling frame. From each sub-region, four countries were randomly selected (probability proportional to population size). From each country, two provinces in addition to capital city were randomly selected. From each province, seven health facilities were randomly chosen from the health facilities with more than 1000 births per year and having ability to perform CS. In the WHOMCS, all WHOOGS countries were invited to participate, however only 22 countries were able to participate. Two countries (Cuba and Algeria) were unable to participate. Within the remaining 22 countries, 32 facilities with very poor recruitment, data quality issues, or that were unable to participate were not included in the WHOMCS. Seven new countries (Afghanistan, Pakistan, Occupied Palestinian Territories, Mongolia, Jordan, Qatar and Lebanon) were added to improve global representation, bringing the total to 29 countries in WHOMCS.

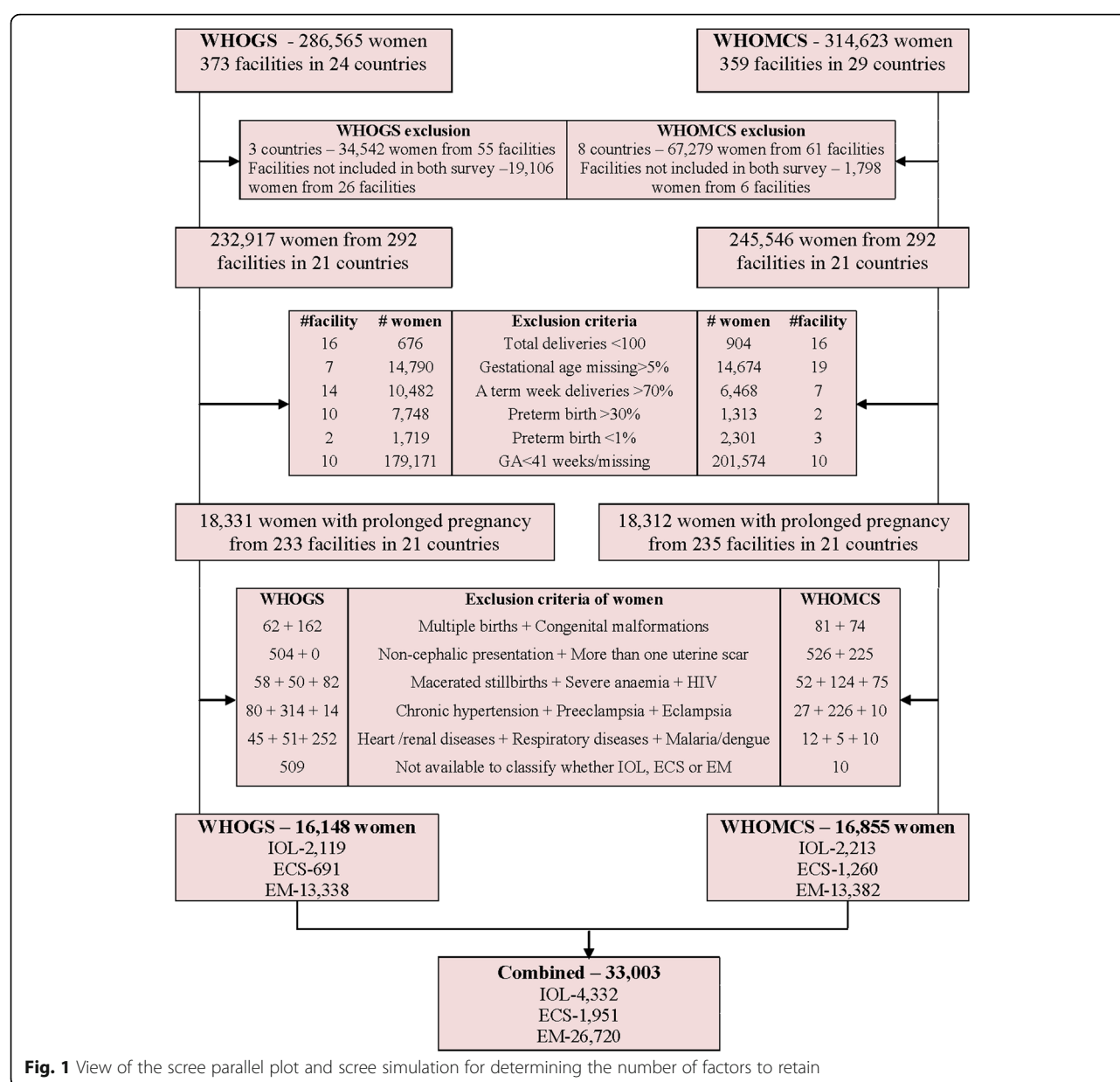
Data in both surveys were collected using individual and institutional case record forms. Data were captured from the time the women first attended at facility for delivery until death, discharge or seventh postpartum day (whichever occurred first). Adverse pregnancy outcomes that occurred after discharge, during referral or after seventh postpartum day were not recorded. Data collection period was two months in health facilities with at least 6000 deliveries per year and three months in health facilities with less than 6000 deliveries per year. Socio-demographic characteristics, obstetric history, mode of delivery, labour characteristics and maternal and perinatal outcomes were collected for all women using pre-tested case record forms by trained data collectors. Health facility data concerning available obstetric and newborn services were also recorded in pre-tested institutional forms after consulting the head of department of obstetrics. Web-based data management systems were used for data entry of both databases. Internal consistency of data was randomly cross-checked comparing collected data and hospital records.

The technical content of both protocols was reviewed by specialist panels at the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction. The Specialist Panel on Epidemiological Research reviewed and approved the WHOOGS study protocol for technical content; the Research Project Review Panel (name of panel was changed in 2010) reviewed and approved the technical content of the WHOMCS.

The WHOOGS and the WHOMCS addressed different primary research questions, but both studies used a common list of core variables that enabled this secondary analysis. Some countries and facilities did not participate in both surveys; therefore, we restricted our analysis to the facilities and the countries that contributed data to both databases. Under this restriction, Cuba and Algeria from WHOOGS and Afghanistan, Lebanon, Mongolia, Occupied Palestinian Territory, Pakistan, Qatar and Jordan from WHOMCS were excluded. Angola was excluded from this analysis due to concerns regarding poor data quality for gestational age (a critical variable for this analysis). A total of 21 countries participated in this analysis. Of these 21 countries 26 facilities from WHOOGS and 6 facilities from WHOMCS were not included in both surveys, hence, excluded in this analysis. In addition, the facilities with unreliable information on gestational age distribution (i.e., facilities in which gestational age missing more than 5%, more than 70% of all deliveries occurred at a specific week, or where more than 30% or less than 1% of all deliveries were preterm) and with less than 100 total deliveries were excluded. Details on exclusion of women, facilities and countries are presented in Fig. 1. The current analysis has an analytical approach where three different procedures for managing low risk pregnancies at 41 completed weeks were evaluated in the same setting of 292 facilities in 21 countries.

Study population

At the individual level, women with GA <41 weeks or missing data were excluded. A total of 18,331 women from 233 facilities of WHOOGS and 18,312 women from 235 facilities of WHOMCS were identified as prolonged pregnancies (women with GA $\geq$ 41 completed weeks of gestation). From this cohort of pregnant women, those with two or more previous CS, abnormal fetal presentation, pregnancy complications (preeclampsia, eclampsia), associated systemic diseases (heart disease, lung disease, renal disease, HIV/AIDS, malaria/dengue, severe anaemia (Hb < 7 g/L), and chronic hypertension) and women who delivered multiple births, babies with congenital malformation or macerated stillbirths were excluded. We excluded macerated stillbirths because



they occurred before and were not consequences of IOL. Details are shown in Fig. 1.

In both surveys, we classified women using consistent definitions. Eligible women were classified into three groups based on the management at and beyond 41 completed weeks of gestation. Women who delivered their babies following IOL at 41 completed weeks were considered as the IOL group. Women of IOL group could deliver vaginally or by CS depending on whether the induction was successful or not. Women who delivered by ECS at 41 completed weeks in WHOCS and women delivered by prelabour CS at 41 completed weeks in WHOMCS were considered as ECS group. Women who delivered by spontaneous onset of labour

at 41 completed weeks and all women who delivered beyond 41 completed weeks (regardless of final mode of delivery) were considered as EM group. In this study, vaginal delivery included both normal and instrumental deliveries.

Pregnancy outcomes and other variables

We classified pregnancy outcomes into maternal and perinatal outcomes. For maternal adverse outcomes we assessed postpartum haemorrhage (PPH), uterine rupture, admission to maternal ICU, maternal postpartum length of stay >7 days and severe maternal outcome. CS rate was also compared between IOL and EM groups. Postpartum haemorrhage, uterine rupture and severe

maternal outcome were defined by different criteria for the two databases (as somewhat different variables were available on maternal outcomes). We presented these criteria for each database in Table 1.

Perinatal adverse outcomes included stillbirth, early neonatal death, perinatal death, Apgar scores less than 7 at 5 min and admission to the neonatal intensive care unit (NICU).

Potential confounding factors were considered at both individual and facility levels. At the individual level, these included maternal age, education, marital status, parity, previous CS and birth weight. At the facility level, the availability of maternal healthcare services was classified into different levels, called facility capacity index (FCI) score. FCI score was calculated by using basic and essential services available at that facility and slightly different between WHOOGS [21] and WHOMCS (due to differences in the institutional form used in the surveys) [22]. For consistency, we used FCI score calculated from WHOMCS in our analysis. It was ranged from 12 for the least resource service facility to 57 for the highest resource service facility. FCI score was used as a continuous variable and adjusted as a facility level covariate.

Statistical analysis

We used frequency to describe maternal and neonatal characteristics of the three sub-populations for analysis in both surveys. Comparisons of maternal and neonatal characteristics among different management groups were done using chi-square test. Multilevel logistic regression model was used to assess associations of different management groups with each pregnancy outcome, adjusted for the potential confounding factors and hierarchical survey design, using two levels (individual and facility level) for separate analysis of WHOOGS and WHOMCS. For the combined database, source of data (WHOOGS and WHOMCS) was used as an additional level. Risks of maternal and neonatal adverse outcomes associated with each management group were assessed separately for WHOOGS, WHOMCS and the combined database to identify the any consistency of associations. The results were presented by crude and adjusted odds ratios (crude ORs and AORs) with corresponding 95% confidence intervals (95% CIs). IOL group was used as a

reference group because this is the procedure currently recommended by WHO [1]. Statistical analyses were done using lme4 package [23] in R software [24].

Results

The prevalence of prolonged pregnancy at facility setting in WHOOGS, WHOMCS and combined databases were 7.9% (18,331/232917), 7.5% (18,312/245546) and 7.7% (36,643/478463), respectively.

A total of 33,003 singleton pregnant women (16,148 women from WHOOGS and 16,855 women from WHOMCS) with prolonged pregnancy (≥ 41 completed weeks) were included in this analysis. Median gestational age for this cohort was 41 and 95% CIs were 41–43 weeks. Amongst them, 13.1% ($n = 4332$) were delivered by IOL, 5.9% ($n = 1951$) were delivered by elective or prelabour CS and 80.9% ($n = 26,720$) were in EM group. Details are presented in Fig. 1.

The details of maternal and neonatal characteristics among the three different management groups for WHOOGS and WHOMCS are presented in Table 2. We found that pregnant women were significantly different with respect to maternal age, education, parity, previous CS and newborns birth weight among the three different management groups in both WHOOGS and WHOMCS but marital status was significantly different only in WHOOGS.

Adverse maternal outcomes among different management groups

Table 3 showed comparison of adverse maternal outcomes among different management groups for WHOOGS, WHOMCS and combined database, respectively. The association could not be assessed for ruptured uterus and ICU admission outcomes in WHOMCS as women with these outcomes were found only in EM group. In combined database, increased risk of ruptured uterus outcome was not statistically significant for EM compared to IOL (aOR 1.98; 95% CI: 0.51–7.65). EM was significantly associated with decreased risk of CS rate consistently in both databases i.e. (aOR 0.76; 95% CI: 0.66–0.87) in WHOOGS, (aOR 0.67; 95% CI: 0.59–0.76) in WHOMCS and (aOR 0.70; 95% CI: 0.64–0.77) in combined database, compared to IOL.

Table 1 Criteria used to define maternal outcomes in WHOOGS and WHOMCS databases

Maternal Outcomes	WHOOGS Database	WHOMCS Database
Uterine rupture	Women who had laparotomy for uterine rupture or delivered by CS due to suspected/imminent uterine rupture	Women with complication of ruptured uterus
PPH	Women who had blood transfusion due to PPH or received uterotronics as a treatment of PPH	Women with complication of PPH
Severe maternal outcome	Women who had experienced in any of death or severe maternal morbidity – blood transfusion, hysterectomy, ICU admission and eclampsia	Women who had experienced maternal death or maternal near miss according to WHO criteria [20]

Table 2 Maternal and neonatal characteristics of three different management groups for WHOOGS and WHOMCS databases

Variables	WHOOGS (N = 16,148) Different management groups			P value	WHOMCS (N = 16,855) Different management groups			P value
	IOL (N = 2119) n (%)	ECS (N = 691) n (%)	EM (N = 13,338) n (%)		IOL (N = 2213) n (%)	ECS (N = 1260) n (%)	EM (N = 13,382) n (%)	
Maternal characteristics								
Age (Years)								
≤ 19	168 (7.9)	53 (7.7)	1578 (11.8)	< 0.001	222 (10.0)	104 (8.3)	1532 (11.5)	0.003
20–34	1786 (84.3)	571 (82.6)	10,623 (79.7)		1801 (81.4)	1035 (82.1)	10,606 (79.3)	
≥ 35	165 (7.8)	67 (9.7)	1137 (8.5)		190 (8.6)	121 (9.6)	1244 (9.3)	
Education (School years)								
< 7	412 (20.0)	119 (17.3)	3218 (24.3)	< 0.001	290 (13.1)	195 (15.4)	2854 (21.3)	< 0.001
7–12	1173 (56.9)	409 (59.4)	7842 (59.3)		1151 (52.0)	728 (57.8)	7671 (57.3)	
> 12	476 (23.1)	161 (23.4)	2176 (16.4)		772 (34.9)	337 (26.8)	2857 (21.4)	
Marital								
With partner	1954 (92.3)	620 (90.0)	11,663 (87.5)	< 0.001	1944 (87.8)	1119 (88.8)	11,812 (88.3)	0.692
Without partner	164 (7.7)	69 (10.0)	1660 (12.5)		269 (12.2)	141 (11.2)	1570 (11.7)	
Parity								
Primiparous	1223 (57.7)	372 (53.8)	6353 (47.6)	< 0.001	1304 (59.0)	797 (63.3)	6496 (48.6)	< 0.001
Multiparous	896 (42.3)	319 (46.2)	6985 (52.4)		908 (41.0)	462 (36.7)	6879 (51.4)	
Previous CS								
Yes	43 (2.0)	171 (24.7)	731 (5.5)	< 0.001	75 (3.4)	259 (20.7)	879 (6.6)	< 0.001
No	2076 (98.0)	520 (75.3)	12,607 (94.5)		2135 (96.6)	993 (79.3)	12,480 (93.4)	
Neonatal characteristics								
Birth weight								
< 2500 g	57 (2.7)	9 (1.3)	359 (2.7)	< 0.001	71 (3.2)	33 (2.6)	448 (3.4)	< 0.001
2500–4000 g	1970 (93.0)	585 (84.7)	12,220 (91.6)		2017 (91.1)	1084 (86.0)	12,208 (91.2)	
> 4000 g	92 (4.3)	97 (14.0)	758 (5.7)		125 (5.7)	143 (11.4)	726 (5.4)	

(IOL Induction of labour group, ECS Elective Caesarean section group, EM Expectant management group)

Adverse perinatal outcomes among different management groups

Use of ECS was significantly associated with increased risks of NICU admission, aOR 1.76; 95%CI: 1.28–2.42 in WHOMCS and aOR 1.51; 95%CI: 1.19–1.92 in combined database, compared to IOL. The association was not statistically significant in WHOOGS database. Apart from NICU outcome, the rest of perinatal outcomes were not significantly associated with different management groups. Details are presented in Table 4.

One consideration in this analysis is that some women in the EM group may experience induction and/or CS at a later gestational age. To account for this, we re-classified those women in the EM group (at 41 completed weeks) who experienced induction or ECS later in pregnancy (i.e. beyond 41 completed weeks). There were 1759 pregnant women in the EM group with deliveries at beyond 41 weeks of gestation. They could be classified to IOL group for 1217 women and ECS group for 542 women. We did sensitivity

analyses of the associations of the new classification of management groups with each pregnancy outcome in the combined database. The results showed consistent findings with our main analysis. In addition the sensitivity analyzed results provided stronger associated with increased risk of postpartum length of stay >7 days outcome (aOR1.59; 95% CI: 1.17–2.18) and admission to NICU outcome (aOR1.54; 95% CI: 1.25–1.90) for ECS compared to IOL. The stronger associated with decreased risk of severe maternal outcome (aOR0.73; 95% CI: 0.55–0.99), rate of CS (aOR0.65; 95% CI: 0.59–0.70) and admission to NICU outcome (aOR0.84; 95% CI: 0.72–0.97) were also seen for EM compared to IOL. Details are presented in Table 5. We also assessed the risk of stillbirths by week delivered using 41 weeks as a reference group. The risk was not significantly different at 42 weeks (aOR1.47; 95% CI: 0.82–2.62). However, as gestational age reached 43, 44 and 45 weeks, the risk of stillbirth were significantly increased, aOR3.45; 95% CI: 1.32–9.03 for 43 weeks, aOR 6.15; 95% CI: 1.38–27.48

Table 3 Adverse maternal outcomes among different management groups in WHOGS, WHOMCS and Combined databases

Adverse maternal outcomes	WHOGS		WHOMCS		Combined	
	n/N (%)	Crude OR ^a (95% CI)	AOR ^b (95% CI)	n/N (%)	Crude OR ^a (95% CI)	AOR ^b (95% CI)
PPH						
IOL	88/2119 (4.2)	1	1	38/2213 (1.7)	1	1
ECS	11/691 (1.6)	0.78 (0.39, 1.56)	0.66 (0.30, 1.44)	19/1260 (1.5)	1.01 (0.54, 1.87)	0.99 (0.50, 1.98)
EM	542/13338 (4.1)	1.12 (0.84, 1.51)	1.21 (0.86, 1.70)	173/13382 (1.3)	0.88 (0.58, 1.33)	0.91 (0.57, 1.45)
Ruptured uterus						
IOL	3/2119 (0.5)	1	1	0/2213 (0.0)	–	–
ECS	2/691 (0.3)	0.65 (0.10, 4.04)	0.40 (0.05, 3.22)	0/1260 (0.0)	–	–
EM	40/13338 (1.2)	2.70 (0.79, 9.28)	1.52 (0.32, 7.16)	10/13382 (0.1)	–	–
Admission to ICU						
IOL	24/2119 (1.1)	1	1	0/2213 (0.0)	–	–
ECS	5/691 (0.7)	1.85 (0.58, 5.88)	1.17 (0.35, 4.03)	0/1260 (0.0)	–	–
EM	258/13338 (1.9)	0.62 (0.37, 1.03)	0.60 (0.34, 1.03)	8/13382 (0.1)	–	–
Postpartum length of stay >7 days						
IOL	76/2119 (3.6)	1	1	44/2213 (2.0)	1	1
ECS	21/691 (3.0)	2.18 (1.29, 3.68)	1.22 (0.68, 2.19)	49/1260 (3.9)	2.33 (1.51, 3.60)	1.54 (0.96, 2.49)
EM	373/13338 (2.8)	1.08 (0.80, 1.45)	0.98 (0.71, 1.35)	424/13382 (3.2)	0.81 (0.57, 1.15)	0.83 (0.57, 1.21)
Severe maternal outcome ^c						
IOL	52/2119 (2.5)	1	1	4/2213 (0.2)	1	1
ECS	14/691 (2.0)	1.41 (0.73, 2.70)	1.15 (0.57, 2.34)	3/1260 (0.2)	1.41 (0.30, 6.63)	0.64 (0.10, 3.97)
EM	382/13338 (2.9)	0.80 (0.56, 1.14)	0.86 (0.59, 1.27)	18/13382 (0.1)	0.67 (0.21, 2.13)	0.55 (0.16, 1.79)
CS rate						
IOL	590/2119 (27.8)	1	1	690/2213 (31.2)	1	1
EM	3416/13338 (25.6)	0.82 (0.73, 0.92)	0.76 (0.66, 0.87)	3463/13382 (25.9)	0.69 (0.61, 0.77)	0.67 (0.59, 0.76)
					0.74 (0.68, 0.80)	0.70 (0.64, 0.77)

(IOL Induction of labour group, ECS Elective Caesarean section group, EM Expectant management group) ^aCrude ORs were calculated by multilevel logistic regression model after accounted for cluster effect (facility level and country level) ^bAdjusted – for maternal characteristics (age, marital status, education, parity, previous CS); neonatal characteristics (birth weight); facility capacity index score and cluster effect (health facility level, country level in WHOGS and WHOMCS; one more level (data source – WHOGS & WHOMCS) in combined database ^cSevere maternal outcome – presence of at least one of maternal death, blood transfusion, hysterectomy, eclampsia and admission to ICU in WHOGS; presence of maternal death or maternal near miss in WHOMCS (Maternal near miss is defined as WHO criteria) Values in bold mean they are statistically significant ($p < 0.05$)

Table 4 Adverse perinatal outcomes among different management groups in WHOGS, WHOMCS and Combined databases

Adverse perinatal outcomes	WHOGS		WHOMCS		Combined	
	n/N (%)	Crude OR ^a (95% CI)	AOR ^b (95% CI)	n/N (%)	Crude OR ^a (95% CI)	AOR ^b (95% CI)
APGAR <7 at 5 min						
IOL	40/2119 (1.9)	1	1	23/2213 (1.1)	1	1
ECS	3/691 (0.4)	0.39 (0.12, 1.22)	0.31 (0.08, 1.23)	13/1260 (1.0)	1.20 (0.61, 2.36)	0.92 (0.45, 1.90)
EM	309/13338 (2.3)	1.10 (0.77, 1.57)	1.21 (0.82, 1.81)	232/13382 (1.8)	1.41 (0.91, 2.20)	1.39 (0.88, 2.19)
Admission to NICU						
IOL	146/2119 (6.9)	1	1	101/2213 (4.6)	1	1
ECS	67/691 (9.7)	1.61 (1.15, 2.26)	1.13 (0.75, 1.72)	117 /1260 (9.3)	1.99 (1.47, 2.71)	1.76 (1.28, 2.42)
EM	1035/13338 (7.8)	0.94 (0.76, 1.15)	0.99 (0.79, 1.26)	587/13382 (4.4)	0.90 (0.71, 1.15)	0.92 (0.72, 1.18)
Stillbirth						
IOL	10/2119 (0.5)	1	1	8/2213 (0.4)	1	1
ECS	0/691 (0.0)	–	–	4 /1260 (0.3)	1.06 (0.31, 3.62)	0.99 (0.27, 3.57)
EM	47/13338 (0.4)	0.69 (0.33, 1.46)	0.63 (0.29, 1.38)	73/13382 (0.6)	1.29 (0.60, 2.78)	1.29 (0.56, 2.98)
Early neonatal death						
IOL	2/2119 (0.1)	1	1	7/2213 (0.3)	1	1
ECS	1/691 (0.1)	2.25 (0.20, 25.5)	2.10 (0.18, 24.7)	4 /1260 (0.3)	1.23 (0.35, 4.35)	0.95 (0.26, 3.45)
EM	50/13338 (0.4)	4.17 (0.99, 17.5)	3.82 (0.89, 16.2)	67/13382 (0.5)	1.28 (0.57, 2.91)	1.11 (0.48, 2.56)
Perinatal death						
IOL	12/2119 (0.6)	1	1	15/2213 (0.7)	1	1
ECS	1/691 (0.1)	0.42 (0.06, 3.02)	0.41 (0.05, 3.10)	8 /1260 (0.6)	1.15 (0.50, 2.66)	0.96 (0.40, 2.30)
EM	97/13338 (0.7)	1.27 (0.68, 2.36)	1.18 (0.62, 2.22)	139/13382 (1.0)	1.20 (0.70, 2.05)	1.14 (0.65, 2.02)

(IOL Induction of labour group, ECS Elective Caesarean section group, EM Expectant management group) ^aCrude ORs were calculated by multilevel logistic regression model after accounted for cluster effect (facility level and country level) ^bAdjusted – for maternal characteristics (age, marital status, education, parity, previous CS); neonatal characteristics (birth weight); facility capacity index score and cluster effect (health facility level, country level in WHOGS and WHOMCS; one more level (data source – WHOGS & WHOMCS) in combined database Values in bold mean they are statistically significant ($p < 0.05$)

Table 5 Adverse maternal and perinatal outcomes among different management groups in combined databases (Sensitivity analysis)

	Combined		
	n/N (%)	Crude OR ^a (95% CI)	AOR ^b (95% CI)
Adverse maternal outcomes			
PPH			
IOL	168/5549 (3.03)	1.0	1.0
ECS	45/2493 (1.81)	0.98 (0.69, 1.40)	0.90 (0.61, 1.33)
EM	658/24,961 (2.64)	0.87 (0.71, 1.06)	0.88 (0.70, 1.11)
Ruptured uterus			
IOL	5/5549 (0.14)	1.0	1.0
ECS	2/2493 (0.08)	0.42 (0.09, 1.79)	0.21 (0.04, 1.06)
EM	48/24,961 (0.31)	2.72 (1.18, 6.25)	1.25 (0.45, 3.45)
Admission to ICU			
IOL	32/5549 (0.58)	1.0	1.0
ECS	9/2493 (0.36)	2.06 (1.01, 4.21)	1.56 (0.65, 3.76)
EM	254/24,961 (1.02)	0.78 (0.52, 1.15)	0.72 (0.45, 1.14)
Postpartum stay > 7			
IOL	154/5549 (2.78)	1.0	1.0
ECS	101/2493 (4.05)	2.48 (1.87, 3.29)	1.59 (1.17, 2.18)
EM	732/24,961 (2.93)	0.97 (0.79, 1.18)	0.92 (0.74, 1.15)
Severe maternal outcome			
IOL	79/5549 (1.42)	1.0	1.0
ECS	24/2493 (0.96)	1.50 (0.94, 2.40)	1.18 (0.71, 1.96)
EM	370/24,961 (1.48)	0.72 (0.54, 0.94)	0.73 (0.55, 0.99)
CS rate			
IOL	1591/5549 (28.67)	1.0	1.0
EM	6026/24,961 (24.14)	0.70 (0.65, 0.75)	0.65 (0.59, 0.70)
Adverse perinatal outcomes			
APGAR <7 at 5 min			
IOL	109/5549 (1.97)	1.0	1.0
ECS	29/2493 (1.17)	0.86 (0.56, 1.30)	0.67 (0.41, 1.08)
EM	482/24,961 (1.94)	0.88 (0.70, 1.10)	0.97 (0.76, 1.24)
Admission to NICU			
IOL	344/5549 (6.22)	1.0	1.0
ECS	257/2493 (10.31)	1.89 (1.57, 2.29)	1.54 (1.25, 1.90)
EM	1452/24,961 (5.83)	0.82 (0.72, 0.94)	0.84 (0.72, 0.97)
Stillbirth			
IOL	25/5549 (0.45)	1.0	1.0
ECS	7/2493 (0.28)	0.91 (0.40, 2.08)	0.76 (0.30, 1.91)
EM	110/24,961 (0.44)	0.94 (0.60, 1.48)	1.01 (0.62, 1.65)
Early neonatal death			
IOL	23/5549 (0.42)	1.0	1.0
ECS	7/2493 (0.28)	0.91 (0.39, 2.08)	0.71 (0.30, 1.68)
EM	101/24,961 (0.41)	0.93 (0.59, 1.48)	0.82 (0.51, 1.32)
Perinatal death			

Table 5 Adverse maternal and perinatal outcomes among different management groups in combined databases (Sensitivity analysis) (*Continued*)

	Combined		
	n/N (%)	Crude OR ^a (95% CI)	AOR ^b (95% CI)
IOL	48/5549 (0.87)	1.0	1.0
ECS	14/2493 (0.56)	0.93 (0.51, 1.69)	0.75 (0.39, 1.43)
EM	210/24,961 (0.84)	0.92 (0.66, 1.27)	0.90 (0.63, 1.27)

IOL Induction of labour group, *ECS* Elective Caesarean section group, *EM* Expectant management group

^aCrude ORs were calculated by multilevel logistic regression model after accounted for cluster effect (facility level, country level, data source -WHOGS & WHOMCS)

^bAdjusted for maternal characteristics (age, marital status, education, parity, previous CS); neonatal characteristics (birth weight); facility capacity index score and cluster effect (facility level, country level, data source - WHOGS & WHOMCS)

for 44 weeks and aOR18.04; 95% CI: 1.96–166.11 for 45 weeks. Details are presented in Table 6.

Discussion

The prevalence of prolonged pregnancy was about 8% of total deliveries. The prevalence of prolonged pregnancy varies across the world from 3 to 12% [25] and our analysis supports those findings. The prevalence is affected by accuracy of gestational age estimation and adoption of elective induction of labour before 41 weeks of gestation [8]. The risk of stillbirth increased significantly when gestational age was 43 weeks or over compared to 41 weeks.

ECS was significantly associated with increased risk of adverse perinatal outcomes compared to IOL for NICU admission in WHOMCS and combined databases. Compared to IOL, EM was significantly associated with decreased risk of CS consistently in all three databases.

Four previous systematic reviews [12, 14–16] reported the effect of IOL compared to EM among prolonged/post-term pregnancies. Systematic reviews of Wennerholm et al., 2009 [15] and Sanchez-Ramos et al., 2003 [16] reported no significant difference in perinatal deaths while those of Gülmezoglu et al., 2012 (Cochrane review) [12] and Hussain et al., 2011 [14] reported significantly lower perinatal death in IOL group. Three systematic reviews i.e. Sanchez-Ramos et al., Wennerholm et al. and Gülmezoglu et al. reported significant lower CS delivery rate in IOL compared to EM. These reviews support the WHO recommendation of routine use of IOL for pregnancies at 41 completed weeks. Our analysis of routinely collected data showed no significant difference in perinatal deaths, however there was a significant lower CS rate in EM compared to IOL in all databases. Possible explanations include: (1) in the Cochrane review, number of perinatal deaths were very small (only 10 deaths) but perinatal death rate of EM was 8 times more than IOL (0.32% vs. 0.04%). In our

Table 6 Risk of stillbirth by week delivered

Stillbirth	Combined	Crude OR ^a (95% CI)	AOR ^b (95% CI)
	n/N (%)		
41 completed week	95/25,631 (0.37)	1.0	1.0
42 completed week	32/6335 (0.51)	1.15 (0.76, 1.71)	1.47 (0.82, 2.62)
43 completed week	10/829 (1.21)	2.91 (1.52, 5.58)	3.45 (1.32, 9.03)
44 completed week	3/157 (1.91)	4.36 (1.39, 13.64)	6.15 (1.38, 27.48)
45 completed week	2/51 (3.92)	11.12 (2.72, 45.41)	18.04 (1.96, 166.11)

^aCrude ORs were calculated by multilevel logistic regression model after accounted for cluster effect (facility level, country level, data source -WHOGS & WHOMCS)

^bAdjusted for maternal characteristics (age, marital status, education, parity, previous CS); neonatal characteristics (birth weight); facility capacity index score and cluster effect (facility level, country level, data source - WHOGS & WHOMCS)

analysis, perinatal death was more common (272 deaths) but perinatal death rate of EM was only 1.4 times more than IOL (0.88% vs. 0.62%), (2) our results were from hierarchical databases and we adjusted for multiple potential confounders and clustering effects of facility and country levels in the analysis, this could lead to more conservative confidence interval and (3) the number of participants in the Cochrane review were quite similar across comparison groups but that of our study groups were quite different in number. One more explanation for the difference between our findings and the systematic reviews may relate to difference in context. Trials are generally conducted in highly controlled, often ideal settings (and often in high-resource settings), which may favour efficacy. Our data relates more to real-life practices (i.e. effectiveness) in resource-limited settings, where the intervention may not be as beneficial as trials might suggest. A recently published before and after study comparing a policy induction of labour at 41 weeks versus at 42 weeks showed a significantly lower CS rate, 15% versus 19.4% ($p = 0.0135$) in a 41-week policy. There were no significant differences in maternal or neonatal outcomes [26].

In spite of our extensive literature search, we did not identify any studies comparing IOL and ECS for women at or beyond 41 completed weeks of gestation. Similar with our results, previous study conducted among women at all gestational ages also showed that CS increased the risk of maternal and neonatal adverse outcomes [17].

To our knowledge, this analysis was the first report of the adverse pregnancy outcomes of ECS among women with prolonged pregnancy. This study was based on two large WHO databases conducted in Africa, Asia, Latin America and the Middle East regions. Data were systematically collected by trained personnel. Thus the results of this study reflect the actual practices in participating facilities and their pregnancy outcomes in these facilities.

However, the WHO databases were collected for other specific objectives rather than to explore our

study question. Moreover, the two surveys used slightly different case record forms to collect individual and institutional characteristics. Consequently, a few adverse outcomes (postpartum haemorrhage, uterine rupture and severe maternal outcome) had slightly different definitions. Despite this, we elected to combine the databases and analyzed these outcomes collectively as we regarded the outcomes as sufficiently similar.

Both databases were facility based, conducted mainly in larger, secondary and tertiary facilities where CS was available – this might lead to over-representation of adverse outcomes among women and their newborns. Thus, this study results might not be representative in smaller or different facilities. The primary data source was routine hospital records; these may not be ideal in many facility settings. Some facilities encountered sub-optimal record collection such as lack of documented diagnosis. It may be due to inability to diagnose condition, failure to recognize condition or failure to document diagnosis, rather than absence of condition. To address this, several facilities adopted the study data collection form as a platform for their medical records. In the WHOMCS, in cases of unclear or missing information, medical staffs were asked to clarify information in the medical record.

The gestational age used was the best obstetric estimate based on local practices. The method of GA assessment was unknown; but usually included the calculation from last menstrual period and/or ultra-sonographic examination. Inaccurate estimate of gestational age can lead to over-estimate prolonged pregnancy [27] and thus may have affected the results of this analysis. However, this misclassification would bias the risk assessment toward unity. The risk that we have estimated should be more conservative. We also tried to minimize the effect of gestational age inaccuracy on this analysis by excluding facilities with GA missing >5% and with unreliable information on gestational age distribution such as more than 70% of all deliveries occurred at a specific week, or where more than 30% or less than 1% of all deliveries were preterm (Fig. 1). Furthermore, data concerning

with methods, types of drugs and routes of administration for IOL cervical ripening methods, oxytocin augmentation protocols, use of partogram, use of electronic fetal monitoring and epidural analgesia rates were not available in databases, so, we could not adjust for these variations to evaluate the outcomes of IOL group.

The differences in institutional intrapartum practices might influence the pregnancy outcomes. We used multilevel logistic regression model to account this effect and hierarchical survey design, using two levels (individual and facility level) for separate analysis of WHOGS and WHOMCS. Moreover, two WHO surveys conducted at different time period and the intrapartum practices of the same facilities might change in two surveys. We accounted for this effect, source of data (WHOGS and WHOMCS) as an additional level for the analysis in combined database.

In addition we did the sensitivity analyses and it showed similar associations among the three management groups when some women were reclassified based on their management beyond 41 weeks of gestation. The other limitation of this study is that it was hospital based and didn't have information on those women who didn't come to the hospital for delivery.

Conclusions

Compared to IOL, ECS significantly increased risk of NICU admission while EM was significantly associated with decreased risk of CS. ECS should not be recommended for women at 41 completed weeks of pregnancy without spontaneous pain. However, the choice between IOL and EM should be cautiously considered since the available evidences are still quite limited.

Abbreviations

AIDS: Acquired Immune Deficiency Syndrome; CS: Caesarean Section; ECS: Elective Caesarean Section; EM: Expected Management; GA: Gestational age; HIV: Human Immunodeficiency Virus; IOL: Induction of Labour; UNDP: United Nations Development Programme; UNFPA: United Nations Population Fund; UNICEF: United Nations International Children's Emergency Fund; WHO: World Health Organization; WHOGS: World Health Organization Global Survey; WHOMCS: World Health Organization Multicountry Survey

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to they belonged to Department of Reproductive Health and Research, The World Health Organization but could be available from WHO on reasonable request.

Authors' contributions

KSM formulated the research question. KSM, ML and PL developed study protocol and analysis plan. KSM cleaned and analyzed the data. KSM, ML and PL drafted the manuscript. All authors reviewed and approved the final version of the manuscript.

Ethics approval and consent to participate

The WHOGS and WHOMCS were approved by the WHO Ethical Review Committee and the relevant ethical clearance bodies in participating countries and facilities. Written consent from individual women was not needed because there was no contact between the data collectors (who extracted routine medical record data) and individual women, and all data was anonymized.

Consent for publication

Not applicable.

Competing interests

The authors declared that they have no competing interests.

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WHO multicentre study for the development of growth standards from fetal life to childhood: the fetal component

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Abstract

Background: In 2006 WHO presented the infant and child growth charts suggested for universal application. However, major determinants for perinatal outcomes and postnatal growth are laid down during antenatal development. Accordingly, monitoring fetal growth *in utero* by ultrasonography is important both for clinical and scientific reasons. The currently used fetal growth references are derived mainly from North American and European population and may be inappropriate for international use, given possible variances in the growth rates of fetuses from different ethnic population groups. WHO has, therefore, made it a high priority to establish charts of optimal fetal growth that can be recommended worldwide.

Methods: This is a multi-national study for the development of fetal growth standards for international application by assessing fetal growth in populations of different ethnic and geographic backgrounds. The study will select pregnant women of high-middle socioeconomic status with no obvious environmental constraints on growth (adequate nutritional status, non-smoking), and normal pregnancy history with no complications likely to affect fetal growth. The study will be conducted in centres from ten developing and industrialized countries: Argentina, Brazil, Democratic Republic of Congo, Denmark, Egypt, France, Germany, India, Norway, and Thailand. At each centre, 140 pregnant women will be recruited between 8 + 0 and 12 + 6 weeks of gestation. Subsequently, visits for fetal biometry will be scheduled at 14, 18, 24, 28, 32, 36, and 40 weeks (+/- 1 week) to be performed by trained ultrasonographers.

The main outcome of the proposed study will be the development of fetal growth standards (either global or population specific) for international applications.

Discussion: The data from this study will be incorporated into obstetric practice and national health policies at country level in coordination with the activities presently conducted by WHO to implement the use of the Child Growth Standards.

Keywords: Fetal growth, Child development, Ultrasound, Growth standards

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Background

Of the estimated 4 million neonatal deaths each year, more than 60% are associated with low-birth-weight due to intrauterine growth restriction and/or preterm delivery [1]. Accurate prenatal assessment of fetal growth and gestational age to timely identify and adequately manage cases of growth restriction and/or preterm delivery should be considered a public health priority, especially in developing countries where 98% of the worldwide neonatal deaths occur.

Before the advent of ultrasonography, fetal growth was assessed by evaluating newborn weight as the end point of the intrauterine growth process. However, cumulative evidence indicated that this birth weight curve approach did not accurately describe the fetal growth process for newborns born before 37 weeks of pregnancy, and low birth weight babies born at term. In response to this evidence, the prenatal assessment of fetal growth and gestational age *in utero* by means of ultrasonography was adopted as standard practice in prenatal care throughout the world. The adequacy of fetal size is currently assessed by comparing the measurements of fetal anatomical parameters at a given gestational age captured through ultrasonography with reference percentiles of fetal size derived from populations of fetuses whose growth was assumed to be normal. These same reference percentiles can be used to estimate gestational age from observed fetal size. The most commonly used reference charts of size by gestational age were developed based on data from populations of fetuses in the United States or Europe. Since 1981, concerns have been raised that such charts might not be appropriate for use in other ethnic groups which may experience different patterns of fetal growth [2-4]. If fetal growth is dependent upon ethnic heritage, the potential for misclassification of fetal growth abnormalities through the wide-scale application of existing growth reference charts should generate concerns regarding diagnostic and management decisions made on the basis of ultrasonographic fetal growth assessments. Others counter argue that environmental factors play a more critical role in fetal growth than ethnicity, and that all fetuses should undergo comparable growth patterns in the absence of environmental constraints to growth [5]. The need to resolve this debate makes the development of fetal growth standards for international application both timely and a priority for improving maternal, fetal and newborn health care worldwide [6].

Reliable standards of fetal growth are important for assessing the wellbeing of each maternal-infant dyad, determining the health status of populations, and monitoring progress in fetal and newborn health and development. Accurate fetal growth assessment is also important for maternal health. Fetal growth abnormalities are often associated with pregnancy complications such as hypertensive disorders and may affect how specific pregnancies are

managed (e.g. the decision to perform a caesarean section). Thus, the results of this study will be beneficial for maternal and fetal/newborn health, they will support efforts to provide a continuum of care for mothers and their infants, and will be relevant to country efforts to accelerate progress to achieving Millennium Development Goals 1, 4, and 5.

The following sections briefly describe the work done and recommendations issued by the World Health Organization in the field of growth assessment that led to the development of this proposal.

In 2006 WHO released the WHO Child Growth Standards. These curves were the result of the WHO Multi-centre Growth Reference Study (MGRS) [7] which had two characteristics that made the study unique in its field: i) the prescriptive approach [8-10]; ii) the international representation.

The proposed study is an extension of the MGRS to fetal life. It will be based on the same prescriptive approach for sample selection, and will ensure international representation by including populations from five continents. The main outcome of the study, fetal growth reference standards, will complement the MGRS by extending the WHO Child Growth Reference Charts to the prenatal period.

In 2002, a meeting of experts on the life course and health convened by the WHO Department of Non Communicable Diseases and Mental Health, Chronic Diseases and Health Promotion, identified as a top research priority, the "improvement of measures of intra-uterine growth retardation (alternative to low-birth-weight) which must reflect newborn body composition and fetal exposures that may not necessarily be expressed in birth size" [11]. Recent findings relating fetal femur length as assessed *in-utero* by ultrasonography with blood pressure levels in childhood confirm that measures of fetal growth alternative to birth weight provide important information which may help clarify the potential associations between fetal growth abnormalities and postnatal risk of disease [12].

In December 2002, the WHO Department of Nutrition organized a meeting of experts to review current knowledge and the practical implications of the interpretation of birth weight as a health outcome. Further research to develop fetal growth standards was identified as urgent by the group.

Finally, in 1995, the WHO Expert Committee on Physical Status published the results of a three year collaborative effort involving more than 100 experts who reviewed the currently available data on body size and composition at the different stages of life and their interpretation in terms of nutrient intake, activity level and risk of disease [13,14]. As a follow up of these recommendations, WHO implemented and conducted the MGRS. In addition, the WHO Expert Committees also recommended the development of fetal growth reference data suitable for

international applications [5]. The proposed study intends to implement those recommendations as a logical extension of the MGRS.

Methods

Study design

This will be a multi-country observational study aiming at developing fetal growth standards for international application. This study will use an inclusive approach when selecting participating centres so that diverse ethnic population groups and diverse geographic settings are adequately represented. The following centres have been identified to participate in the study based on the proficient use of ultrasonography:

- Argentina: Centro Rosarino de Estudios Perinatales, Rosario
- Brazil: University of Campinas, Campinas
- Democratic Republic of Congo: University of Kinshasa, Kinshasa
- Denmark: Copenhagen University Rigshospitalet, Copenhagen
- Egypt: Assiut University, Assiut
- France: Hôpital Antoine Bécère, Paris
- Germany: University Medical Center, Hamburg
- India: All India Institute of Medical Sciences, New Delhi
- Norway: University of Bergen, Bergen
- Thailand: Khon Kaen University, Khon Kaen

Eligibility criteria

In terms of the selection of a study participant, the protocol will follow a prescriptive approach. Participants with no known health, environmental, and/or socio-economic constraints on fetal growth will be invited to participate in the study if:

- They belong to a high socio-economic status and a high level of parental education, in order to ensure that the curves reflect, as much as possible, the true growth potential of fetuses, by limiting, as much as possible, the influence of environmental factors. Specific cut off points in family income and education have been identified by the MGRS and will be translated into socio-economic indicators specific to the countries participating in the proposed study [9,10,15];
- They live at an altitude lower than 1,500 m;
- They live near the study area. This will ensure compliance with the study, follow up for the study duration, and for potential future follow-up studies in infancy, childhood and eventually adulthood;
- They are 18 years old or more (as younger women are still growing and their babies may be smaller at birth) and ≤ 40 years;

- They have a BMI between 18–30;
- They have a singleton pregnancy;
- Their gestational age at entry is between 8 + 0 to 12 + 6 weeks based on LMP (confirmed by ultrasonography, please see Dating by ultrasound for a more detailed description);
- They have no history of health, environmental or economic constraints likely to impede fetal growth; no need for long-term medication (including fertility treatment); not smoking currently or in the previous 6 months; no history of recurrent miscarriages; and any baby previously delivered pre-term (<37 weeks) or with a birth weight $<2,500$ g (at 37 w 5% of boys and 10% of girls in low-risk pregnancies will be $\leq 2,500$ g);
- There is no evidence in the present pregnancy of congenital disease or fetal anomaly. Participation in the study will cease if a major fetal anomaly is detected or serious illness develops leading to IUGR (birth weight below the 10th percentile of the recommended gender-specific birth weight for gestational age reference curves [16]); however, all mothers recruited will be followed-up until the end of the study for the purposes of describing the whole population.

Study procedure

Women in the first trimester (before 12 + 6 weeks gestation) attending antenatal care clinics providing ultrasonographic examinations will be approached by members of the study team and asked to participate. Women will be fully informed about the study objectives and procedures. Only women who sign a consent form will be enrolled into the study.

Fetuses will be scanned in the first trimester for the estimation of gestational age and subsequently at monthly intervals for fetal biometry [17].

All infants will receive an anthropometrical assessment after delivery, including measurement of birth weight [18]. All pregnant women in the study will be administered a 24-hour dietary recall at entry into the study, and at approximately 28 and 36 weeks gestation, to assess maternal nutritional status and ensure that women enrolled in the study have an adequate diet and that nutrient intake is in accordance with current pregnancy recommendations [18,19]. At each visit, the obstetric history of participating women will be updated to collect information related to pathological processes that may affect fetal growth, and blood pressure and proteinuria will be measured.

No additional procedures will be added to routine antenatal care provided at the study centres, with the exception of 4–5 additional ultrasonographic examinations and three repeat 24-dietary recalls.

Dating by ultrasound

Gestational age will be confirmed by measuring the crown-rump length (CRL) between 8 + 0 to 12 + 6 weeks based on LMP. Gestational age (GA) by CRL should agree with GA by LMP to within 7 days. If LMP and CRL agree, CRL measurement will be used for dating. The average of three measurements will be used. If GA by CRL and GA by LMP differ by more than 7 days, the woman is not eligible for the study.

To acquire the CRL measurements, the midline sagittal section of the whole fetus will be visualized with the fetus horizontal on the screen at 90 degrees to the angle of insonation [20]. GA will be assessed by using the reference charts published by Robinson and Fleming [19].

Fetal biometry

The first visit (dating scan) will be between 8 + 0 and 12 + 6 weeks, and subsequent visits for fetal biometry will be scheduled at approximately 4 weekly (+/- 1 week) intervals at 14, 18, 24, 28, 32, 36, and 40 weeks. All scanning appointments will be arranged at the time of the dating scan and study enrolment. All participants will be scanned in the lateral recumbent position.

The compulsory ultrasound measurements to be obtained at all visits include the following biometrical parameters:

- Biparietal diameter (BPD)
- Head circumference (HC)
- Abdominal circumference (AC)
- Femur length (FL)
- Transcerebellar diameter (TCD)
- Humerus length (HL)
- Fetal Foot length (FFL)

At each examination, all measurements are to be obtained three times from three separately generated ultrasound images and uploaded electronically (with the associated images) to the data management system. The mean of the three measurements of each parameter will be used for clinical management purposes as per local protocols.

In addition, a full morphological evaluation (abnormality scan) will be conducted at 18–24 weeks following standard practices at each centre. Fetuses diagnosed with any minor abnormalities will be managed according to local clinical guidelines. If the clinical decision is to continue with the pregnancy the case will remain in the study. Fetuses with major abnormalities that may affect morphometric measurements will be excluded from further study. All infants will receive an anthropometrical assessment after delivery [21].

The following measurement techniques will be used:

- Biparietal Diameter-Technique: Measured from the outer-outer (BPD 1) and outer – inner (BPD 2) edges of the parietal bones in a cross-sectional view of the fetal head at the level of the thalami and cavum septum pellucidum or cerebral peduncles. The cerebellum is not to be included. The measurement should be obtained from an image with the midline echo as close as possible to the horizontal plane with the angle of insonation of the ultrasound beam at 90 degrees.
- Head Circumference -Technique: Obtained from the same image as BPD as follows: Measurement of occipito-frontal diameter (OFD) obtained by placing calipers on the outer borders of the occipital and frontal edges of the skull at the point of the midline across the longest part of the skull. The ellipse facility will be used to calculate HC as above.
- Abdominal Circumference - Technique: The sonographer will visualize the transverse section of the fetal abdomen as “close as possible” to circular including the stomach and the junction of the umbilical vein and portal sinus. The anterior-posterior (A-P) and transverse diameters will be measured with calipers placed on the outer borders of the body outline. The A-P diameter will be measured from the spine to the anterior abdominal wall and transverse diameter at a right angle to the A-P diameter. The ellipse facility will be used to calculate AC as outlined above.
- FL-Technique: Measured from an image of the full femoral shaft in a plane as close as possible to a right angle to the ultrasound beam. The distal femoral epiphysis is to be excluded.
- Transcerebellar Diameter (TCD): the TCD can be imaged from the sub-occipito-bregmatic view of the fetal skull, and measured from the second trimester onwards. The calipers will be placed on the outer-outer margins of the cerebellar poles.
- Humerus length (HL): Measured from an image of the full humeral shaft in a plane as close as possible to a right angle of insonation.
- Fetal Foot Length (FFL): Fetal foot length will be measured from the second trimester onwards. The foot is measured from either sagittal or plantar views. The measurement is taken from the skin overlying the heel (calcaneus) to the end of the longest toe.

Ultrasound volume acquisition protocol

The ultrasonographic equipment that will be used in the study will allow for acquiring and storing 3-dimensional images. This feature is of critical importance for data quality purposes. Stored 3-dimensional images (volumes)

could be used at a later stage to retake measurements that have been identified as erroneous.

Except for a transvaginal scan during the first research visit (8 0/7 -12 6/7 weeks), 3D volume data will otherwise be acquired using a transabdominal probe. All volumes shall be systematically labelled using the comment feature of the Voluson E8 (GE Healthcare, Germany) Expert system (e.g. "LA1").

Recommended Image settings:

- At least High Quality 2
- CRI no greater than 2
- No speckle reduction (SRI)
- Harmonic imaging as needed
- Acoustic focus adjusted for the anatomic region
- Use the widest image window to capture the volume of interest, depending on fetal activity
- Adjust the magnification and image depth settings to fill at least one-half of the screen

Training

As done in previous studies [3,22] sonographers participating in the study will receive specific training and will be certified as proficient under the supervision of a qualified instructor, according to a standard protocol. Intra-observer and inter-observer measurement errors will be assessed according to a published protocol before the initiation of the study during the training period [21]. We will consider estimating a learning curve [23].

All instruments and techniques to be used in all centres will be standardised, i.e. equipment and training will be provided to each of the measurement teams. Equipment specifications to be considered are the following: i) Commercially available high quality real-time ultrasound scanner; ii) Less than 2 years old; iii) T/V and abdominal probes suitable for scanning throughout pregnancy; iv) Facility for on-line transfer of measurements and associated images; v) Facility to "blind" measurements from examiner until after data transfer.

Site visits to the study centres will be organized in order to provide lectures and update courses by experts in the field. In addition during site visits, standardization sessions will be carried out according to repeat-measure protocols to assess the accuracy and precision of the anthropometrical measurements in mothers and newborns.

Neonatal anthropometrical assessment

Neonatal body composition assessment during the first 24 hours will be used to determine the growth outcome of each pregnancy on the basis of multiple postnatal measurements in order to be able to relate pre- and postnatal anthropometrical measurements. After delivery, a trained investigator will take standardized measurements of the head circumference, abdominal circumference (superior

border of umbilicus), and thigh circumference (at the skin crease located midway between the knee and trunk with the lower leg at about 90 degrees in relation to the thigh measured in centimetres) with non-stretchable tape. The crown-heel length will be obtained by placing the supine infant, with extended legs, on a plastic newborn length board (Stadiometer, Ellard Instrumentation, Seattle, WA, USA). Skin fold caliper measurements (Harpender) will be used to document soft tissue distribution [17,24]. These skin folds will include the triceps fold, anterior thigh fold, sub-scapular skin fold, and abdominal flank skin fold that will be made at each site twice and averaged. This data will be used to estimate per cent body fat and lean body mass as an index of neonatal growth outcome. Other parameters of neonatal body composition will include ponderal index and birth weight [25].

Nutritional assessment

Adequate nutrition is one of the major requirements for selecting populations eligible for the study. Therefore, the assessment and maintenance of adequate nutritional status is considered a critical component of the study activities.

At three times during the study follow-up (at entry and at approximately 28 and 36 weeks) the nurse/nutritionist, trained in collecting anthropometric and diet data, will assess maternal nutritional status *via* anthropometry (weight, height, arm circumference, head circumference, skinfolds) (Table 1), as well as assessing the dietary intake (by twenty-four-hour recall). Measurements will be carried out by a female nurse/nutritionist in a private room according to the procedures described by Gibson [17]. The time of the examination will be recorded to allow for diurnal variations. Having only one person performing the measurements will minimize inter-examiner errors. The equipment required is already available at the study site.

Dietary intakes will be assessed using 24-hour recalls; specifically a trained nutritionist or nurse will query the study participants on foods and beverages consumed by them in the previous 24-hours. Information will also be collected on portion sizes as well as preparation methods. This information will then be linked with appropriate country-specific food composition tables to arrive at estimates of macro and micro-nutrients [27,28]. This method results in the attainment of estimates of the intake of single nutrients. Compliance is high because the respondent burden is low. The interview takes approximately twenty minutes. The quality of the information collected is dependent on the respondent's motivation and ability to recall intakes and on the interviewing skills of the nutritionist/nurse. Repeated twenty-four-hour recalls on the same individual allow estimations of the individual's usual dietary intake over a long period of time [28]. In our study the twenty-four-hour recall will

Table 1 Description of maternal anthropometric measures

Measure	Procedure
Weight	Weight will be measured using a beam balance with nondetachable weights. Weight will be recorded to the nearest 0.1 kg [26].
Height	Height will be measured in the standing position using a stadiometer and recorded to the nearest millimetre. If the reading falls between two values, the lowest millimetre will be recorded [26].
Mid-upper arm circumference	Measurements will be taken using a flexible fiberglass tape wrapped around the upper left arm, at the midpoint between the acromion process and the tip of the olecranon. Measurements will be recorded to the nearest millimetre [26].
Head circumference	A flexible fiberglass tape will be used. The tape will be placed above the supra-orbital ridges and over the part of the occiput which gives the maximum circumference. Measurements will be taken to the nearest millimetre [26].
Skinfolds	Left triceps and left scapular skinfolds will be taken using a Lange skinfold thickness caliper. The combination of one body and one limb skinfold to assess body fat is recommended by most investigators [26].

be repeated three times for each woman. This method has been successfully used in previous studies focusing on nutrition, fetal growth and other pregnancy outcomes conducted by investigators who are taking part in the proposed study.

Safety of ultrasonographic assessment

Ultrasonography in pregnancy is considered a safe procedure and in more than 30 years no fetal harm has been reported with use in the low-intensity range of gray-scale imaging (no Doppler), which is the technology that will be used in the proposed study [29]. Serial ultrasonography for research purposes according to schedules similar to the one we propose has been approved previously in the context of other studies [30-33].

Following a recommendation of the WHO Scientific and Ethical Review Group, we conducted a systematic review and meta-analysis to evaluate the safety of human intrauterine exposure to ultrasonography [32].

We systematically searched electronic databases, reference lists and unpublished literature according to the following criteria:

- Types of studies: Trials and observational studies that assessed short and long term effects of exposure to ultrasonography during pregnancy.
- Types of participants: Women submitted to ultrasonography in pregnancy and their offspring.
- Types of exposure: B-mode or Doppler sonography during any period of pregnancy, for any number of times, using any equipment and transducers.
- Types of outcome measures: 1) adverse maternal outcomes, 2) adverse perinatal outcomes, 3) abnormal childhood neurological development, and 4) childhood malignancies.

The electronic search identified 6716 citations and 63 were selected for full text evaluation. Additionally, 19 citations were identified from secondary sources. A total of 58 references reporting data of 38 different studies

were included: 16 clinical trials, 11 cohorts, and 11 case controls. Ultrasonography in pregnancy was not associated with adverse maternal effects, impaired physical or neurological development or increased risk for malignancies in childhood. According to the clinical trials, there was a weak association between exposure to ultrasonography and non-right handedness in boys (OR 1.26, 95% CI 1.03-1.54) and a slight decrease in mean neonatal length (WMD -0.26 cm, CI -0.45, -0.07) and head circumference (WMD -0.15 cm, CI -0.29, -0.01). In conclusion, based on the available evidence, exposure to diagnostic ultrasonography during pregnancy appears to be safe.

Sample size

The total sample size will be 1400 pregnant women and their infants. Each country centre will collect data from 140 women. This number is sufficient for the development of local centile growth charts with a high level of precision, accounting for exclusions to final analysis due to inability to follow up and occurrence of pregnancy complications [34,35].

The sample size needed for the estimation of a specific percentile was computed using the following formula [36]:

$$n = \frac{(1 + z_{\alpha}^2/2)}{\left(\frac{\%SE P_{\alpha}}{\%CV}\right)^2}$$

where z_{α} is the standard normal deviation corresponding to the percentile being estimated, % SE C_{α} is the expected percentage standard error of the percentile and % CV is the percentage coefficient of variation. Sample sizes were computed for 5 different parameters (biparietal diameter, abdominal and head circumference and femur and humerus length) and for 3 different percentiles: 5%, 10% and 50%. Information about the coefficient of variation was obtained from data on serial ultrasonographic examination conducted on approximately 500 pregnancies in the context of the WHO randomized trial of calcium supplementation in low intake women [37].

Additionally, the expected half-width of the confidence interval with a sample size $n = 100$ was computed.

Table 2 shows the levels of precision obtainable with a sample size of 100 women for various biometrical parameters. In addition the proposed sample size of 140 women per centre will allow for testing for differences in growth patterns across centres [38].

The following table lists, for every biometrical parameter, the number of subjects needed to detect as statistically significant the smallest meaningful difference d with type I error rate of 0.05 and a power of 0.80 with values of

variance (σ^2) and correlation (ρ^2) as estimated using the data from the WHO randomized trial of calcium supplementation in low intake women [37]. The presented sample sizes have been calculated by applying the formula:

$$m = \frac{2(z_\alpha + z_\beta)^2 \sigma^2 (1 - \rho)}{ns_x^2 d^2}$$

Where d is the minimum difference in the rate of change per unit time (week) in the five biometrical parameters by centre, n is the number of visits ($n = 8$) and s_x^2 is

Table 2 Levels of precision obtained with a sample size of 100 women for some biometrical fetal parameters (values and half widths in mm)

Abdominal circumference										
Week	Mean	10% Centile	5% Centile	CV	%SE_50	%SE_10	%SE_5	Width_50	Width_10	Width_5
20	147.7	133.5	128.8	7.9	0.79	1.07	1.21	2.33	2.85	3.12
24	190.7	173.8	166.6	7.4	0.74	1.00	1.14	2.82	3.47	3.78
28	235.2	215.4	210.6	6.4	0.64	0.86	0.98	3.01	3.72	4.13
32	278.6	255.8	248.3	6.5	0.65	0.88	1.00	3.62	4.49	4.95
36	314.5	288.0	277.9	7.1	0.71	0.96	1.09	4.47	5.52	6.05
Biparietal diameter										
Week	Mean	10% Centile	5% Centile	CV	%SE_50	%SE_10	%SE_5	Width_50	Width_10	Width_5
20	46.7	44.0	42.0	5.6	0.56	0.76	0.86	0.52	0.67	0.72
24	59.0	56.0	55.0	4.8	0.48	0.65	0.74	0.57	0.73	0.81
28	70.8	68.0	67.0	3.9	0.39	0.53	0.60	0.55	0.72	0.80
32	80.1	77.0	75.0	3.7	0.37	0.50	0.57	0.59	0.77	0.85
36	87.1	83.0	81.0	3.7	0.37	0.50	0.57	0.64	0.83	0.92
Head circumference										
Week	Mean	10% Centile	5% Centile	CV	%SE_50	%SE_10	%SE_5	Width_50	Width_10	Width_5
20	177.4	164.4	161.2	5.8	0.58	0.78	0.89	2.06	2.57	2.87
24	225.0	212.3	209.2	4.9	0.49	0.66	0.75	2.21	2.81	3.14
28	269.4	254.9	251.8	4.3	0.43	0.58	0.66	2.32	2.96	3.32
32	302.8	286.9	281.6	4.1	0.41	0.55	0.63	2.48	3.17	3.54
36	325.1	308.1	300.1	4.1	0.41	0.55	0.63	2.67	3.41	3.77
Femur length										
Week	Mean	10% Centile	5% Centile	CV	%SE_50	%SE_10	%SE_5	Width_50	Width_10	Width_5
20	32.6	30.0	29.0	6.9	0.69	0.93	1.06	0.45	0.56	0.61
24	43.2	41.0	40.0	4.7	0.47	0.63	0.72	0.41	0.52	0.58
28	53.0	51.0	50.0	3.7	0.37	0.50	0.57	0.39	0.51	0.57
32	61.9	59.0	58.0	3.3	0.33	0.45	0.51	0.41	0.53	0.59
36	69.3	67.0	65.0	3.2	0.32	0.43	0.49	0.44	0.58	0.64
Humerus length										
Week	Mean	10% Centile	5% Centile	CV	%SE_50	%SE_10	%SE_5	Width_50	Width_10	Width_5
20	31.4	28.0	27.0	8.9	0.89	1.20	1.37	0.56	0.67	0.74
24	40.7	38.0	37.0	6.8	0.68	0.92	1.04	0.55	0.70	0.77
28	48.6	45.0	44.0	6.3	0.63	0.85	0.97	0.61	0.77	0.85
32	55.7	52.0	51.0	5.7	0.57	0.77	0.87	0.63	0.80	0.89
36	61.2	57.0	56.0	5.4	0.54	0.73	0.83	0.66	0.83	0.93

the within subject variance [38]. The values of d shown in Table 3 indicate that the sample size needed for the level of precision requested will be very conservative to detect differences in the rate of change between centres.

Data management

Data will be collected *via* an internet based data management system as done with other WHO coordinated studies. The online data collection system will allow for real time solutions of queries or other problems in data collection, such as missing or non-valid data as well as for online checking of images by the international coordination unit.

All data will be stored in a GCP compliant server, and data transmission will be encrypted to assure data integrity and patient confidentiality. Access to the data management web system will be password protected and only authorized users will have access. Data changes will be documented. The system will maintain an audit trail, data trail and edit trail as well as back up of the data.

Data entered into the web system will be checked by the coordinating unit at WHO for completeness, accuracy, reliability and consistent intended performance. The data management team will be responsible for generating the interim and final data report.

These procedures have been used in previous HRP multi-centre trials and proven to be efficient and compliant with the HRP/WHO Standard Operating Procedures as well as with the 21 CFR Part 11 of the Code of Federal Regulations that deals with the United States Food and Drug Administration (FDA) guidelines on electronic records.

Data analysis

Population percentiles will be calculated by applying polynomial regression methods, using the generalized estimating equations method, to model the mean at specific gestational ages, taking into account correlations between repeated measurements on the same subjects [38]. To estimate the standard deviations at each gestational age, we will use the method of the absolute residuals proposed by Altman [39]. This methodology takes into account the increase in variance with advancing gestation typical of fetal biometry data [39]. Differences

in linear growth among populations of different geographical origin (categorized by study site) will be tested by evaluating the proportion of total variability in fetal biometrical measurements attributable to sites and individuals, as well as differences among sites and the effect of excluding sites on the percentiles of the total sample, as done in the MGRS [40]. The same procedure will be used to test for differences in growth related to the sex of the fetus.

Discussion

The data from this study, if findings are similar across diverse populations, may facilitate the adoption of an universal growth standard for international use. If heterogeneity by centre is detected despite selecting study populations according to the prescriptive approach, the study results will indicate the need to develop local/ethnically specific standards.

Technical and ethical approvals

The protocol received technical and ethical approval from the WHO Research Project Review Panel (RP2) and Research Ethics Review Committee respectively as well as from appropriate national and institutional ethic review bodies as applicable for each study centre.

Abbreviations

AC: Abdominal circumference; BMI: Body mass index; BPD: Biparietal diameter; CH: Chest; CRL: Crown rump length; CV: Coefficient of variation; EV: Endovaginal; FFL: Fetal foot length; FL: Femur length; GA: Gestational age; H: Head; HC: Head circumference; HL: Humerus length; ICC: Intraclass correlation coefficient; ISUOG: International Society for Ultrasound in Obstetrics and Gynaecology; IUGR: Intra uterine growth restriction; LA: Lower arm; LL: Lower leg; LMP: Last menstrual period; MDG: Millennium Development Goal; MGRS: Multi-centre Growth Reference Study; OFD: Occipito-frontal diameter; SE: Standard error; TCD: Trans cerebellar diameter; UA: Upper arm; LA: Lower arm; WHO: World Health Organization.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors contributed to the conception and design of the study, read and corrected draft versions of the manuscript and approved the final manuscript.

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Table 3 Estimated sample size and computation assumptions for biometrical parameters

Biometrical parameter	Sample size	Variance	Rho	d (mm)
Biparietal Diameter	32	10.2	0.34	0.1
Head circumference	23	174	0.28	0.5
Abdominal circumference	28	263	0.43	0.5
Femur length	16	5	0.32	0.1
Humerus length	35	11	0.32	0.1

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Use of antenatal corticosteroids and tocolytic drugs in preterm births in 29 countries: an analysis of the WHO Multicountry Survey on Maternal and Newborn Health

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Summary

Background Despite the global burden of morbidity and mortality associated with preterm birth, little evidence is available for use of antenatal corticosteroids and tocolytic drugs in preterm births in low-income and middle-income countries. We analysed data from the WHO Multicountry Survey on Maternal and Newborn Health (WHOMCS) to assess coverage for these interventions in preterm deliveries.

Methods WHOMCS is a facility-based, cross-sectional survey database of birth outcomes in 359 facilities in 29 countries, with data collected prospectively from May 1, 2010, to Dec 31, 2011. For this analysis, we included deliveries after 22 weeks' gestation and we excluded births that occurred outside a facility or quicker than 3 h after arrival. We calculated use of antenatal corticosteroids in women who gave birth between 26 and 34 weeks' gestation, when antenatal corticosteroids are known to be most beneficial. We also calculated use in women at 22–25 weeks' and 34–36 weeks' gestation. We assessed tocolytic drug use, with and without antenatal corticosteroids, in spontaneous, uncomplicated preterm deliveries at 26–34 weeks' gestation.

Findings Of 303 842 recorded deliveries after 22 weeks' gestation, 17 705 (6%) were preterm. 3900 (52%) of 7547 women who gave birth at 26–34 weeks' gestation, 94 (19%) of 497 women who gave birth at 22–25 weeks' gestation, and 2276 (24%) of 9661 women who gave birth at 35–36 weeks' gestation received antenatal corticosteroids. Rates of antenatal corticosteroid use varied between countries (median 54%, range 16–91%; IQR 30–68%). Of 4677 women who were potentially eligible for tocolysis drugs, 1276 (27%) were treated with bed rest or hydration and 2248 (48%) received no treatment. β -agonists alone ($n=346$, 7%) were the most frequently used tocolytic drug. Only 848 (18%) of potentially eligible women received both a tocolytic drug and antenatal corticosteroids.

Interpretation Use of interventions was generally poor, despite evidence for their benefit for newborn babies. A substantial proportion of antenatal corticosteroid use occurred at gestational ages at which benefit is controversial, and use of less effective or potentially harmful tocolytic drugs was common. Implementation research and contextualised health policies are needed to improve drug availability and increase compliance with best obstetric practice.

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Introduction

More than 15 million infants are born preterm every year and preterm birth is the largest cause of death among newborn babies (age up to 28 days) and the second largest cause of death in children younger than 5 years.¹ More than 60% of preterm deliveries occur in Africa and Asia. The deleterious effects of preterm delivery on newborn babies can be mitigated through appropriate use of proven interventions such as antenatal corticosteroids for fetal lung maturation (along with other benefits)² and tocolytic drugs to delay delivery and potentiate the effects of antenatal corticosteroids or allow transfer to a higher-level facility before delivery.³

Injections of corticosteroids before delivery to induce fetal lung maturation and thereby prevent newborn morbidity and mortality has been comprehensively studied for nearly four decades.⁴ The most recent Cochrane review (2006) for use of antenatal corticosteroids in women with preterm delivery included 21 randomised controlled trials of 3885 women and 4269 babies.² Investigators concluded that antenatal corticosteroid use was associated with an overall 31% reduction in neonatal deaths, and significant reductions in risks of respiratory distress syndrome (34%), cerebroventricular haemorrhage (46%), necrotising enterocolitis (54%), need for respiratory support or intensive-care admission (20%), and systemic infections in the first 48 h of life (44%).

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See [Comment](#) page 1829

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Antenatal corticosteroids were effective when given from 26 weeks' to 34 weeks' plus 6 days gestation (even if given less than 24 h before delivery) and did not increase risk of maternal death, chorioamnionitis, or puerperal sepsis. A meta-analysis of the four randomised controlled trials for antenatal corticosteroids for preterm births in middle-income countries suggested that the reduction in mortality might be greater in these countries than in high-income countries.⁵ Benefit of antenatal corticosteroids outside this gestational age range is controversial; however, observational evidence suggests effectiveness when given between 22 weeks' and 26 weeks' gestation,⁶ and investigators of one trial reported that antenatal betamethasone given to women pregnant with term infants reduced neonatal respiratory distress and admission to neonatal special-care units in newborn babies born by elective caesarean section.⁷ Despite the global burden of newborn morbidity and mortality related to preterm births, uptake of antenatal corticosteroids worldwide has been poor—the Bellagio Child Survival Study group⁸ estimated antenatal corticosteroid coverage in 2000 to be just 5% for the 42 countries that had 90% of the world's under-5 deaths. Recent data for worldwide use of antenatal corticosteroids are not available.

Spontaneous preterm labour causes 40–45% of preterm births.⁹ Tocolytic drugs (such as β -agonists, calcium-channel blockers, and oxytocin antagonists) can be used as temporising measures to inhibit labour progression for up to 7 days.^{10–12} Use of tocolytic drugs alone has not been shown to reduce perinatal mortality (although trials have been underpowered for this outcome).³ However, use of the drugs to delay delivery is recommended to permit transfer to a higher-level facility and to potentiate the effects of corticosteroids (and hence should be used in conjunction with antenatal corticosteroids).^{11,12} We did not find any published reports on patterns of tocolytic drug use in preterm labour in low-income and middle-income countries, despite its importance in the management of preterm birth.

We did an analysis of the WHO Multicountry Survey of Maternal and Newborn Health (WHOMCS) dataset for more than 314 000 facility-based deliveries in 29 countries. We aimed to describe patterns of use of antenatal corticosteroids in preterm deliveries and assess the use of tocolytic drugs in spontaneous preterm deliveries.

Methods

Study design and participants

WHOMCS was a cross-sectional, facility-based survey of deliveries between May 1, 2010, and Dec 31, 2011. WHOMCS aimed to characterise severe maternal, perinatal, and neonatal morbidity for a worldwide network of health facilities, with particular focus on WHO maternal near-miss indicators.¹³ Methodological details for WHOMCS have been described elsewhere.^{13,14} Investigators used a stratified, multistage cluster sampling approach to obtain a global sample of countries from

Africa, Asia, Latin America, and the Middle East. Within each country, the capital city was sampled, along with two randomly selected provinces (probability proportional to population). From these areas, seven facilities that had more than 1000 deliveries per year and the capacity to do caesarean sections were randomly selected (if fewer than seven facilities were available, then all were selected). All facilities that were chosen agreed to participate. Data were collected for 2 months in institutions with 6000 or more deliveries every year and for 3 months in institutions with fewer than 6000 deliveries every year. When facilities expected fewer than 3000 deliveries, the data collection period was extended to 4 months.

Study participants were all women who gave birth in participating facilities and women with a severe maternal outcome (death or near-miss) associated with pregnancy, childbirth, or puerperium. Data were obtained prospectively, from time of presentation at the facility until discharge or 7 days post partum (whichever was first). Maternal or perinatal adverse outcomes that occurred after discharge or day 7 or during a post-partum referral were not included. Data collectors reviewed medical records and abstracted de-identified data from records into the individual data form at the time of discharge, transfer, or death. An institutional data form about available obstetric and newborn services was completed in consultation with the head of the department of obstetrics for each facility. Overall, 359 facilities in 29 countries participated in WHOMCS, and data from 314 623 women were recorded. For the purposes of comparison, we defined high-income countries (Japan and Qatar) and low-income and middle-income countries (the remaining 27 countries) according to the World Bank's classification for income group's WHOMCS was approved by the WHO Ethics Review Committee and relevant ethics clearance bodies in participating countries. All authors had access to the WHO Multicountry Survey database; JPV, JPS, and AMG were responsible for the decision to submit the manuscript for publication.

Procedures

WHOMCS captured information about a range of maternal sociodemographic, medical, and obstetric characteristics and outcomes for mothers and newborn babies. The gestational age was recorded in completed weeks on the basis of best available obstetric estimate; the method of estimation was not recorded. Preterm births were defined as infants born before 37 weeks of gestation. The use of antenatal corticosteroids in preterm births was recorded; however, the type, timing, number of doses, and dosing schedule was not. The use of five drug classes as tocolytic drugs for preterm labour was also recorded— β -agonists (eg, terbutaline, ritodrine), non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase (COX) inhibitors (eg, indometacin), calcium-channel blockers (eg, nifedipine), oxytocin antagonists (eg, atosiban), and magnesium sulphate. Use

	Births at 22–25 weeks' gestation (n=497)			Births at 26–34 weeks' gestation (n=7547)			Births at 35–36 weeks' gestation (n=9661)		
	All deliveries	Spontaneous deliveries*†	Provider-initiated deliveries*‡	All deliveries	Spontaneous deliveries†§	Provider-initiated deliveries‡§	All deliveries	Spontaneous deliveries†¶	Provider-initiated deliveries‡¶
Did not receive antenatal corticosteroids	362 (73%)	235 (71%)	112 (77%)	3373 (45%)	2190 (45%)	1163 (45%)	6934 (72%)	5029 (74%)	1894 (67%)
Received antenatal corticosteroids	94 (19%)	69 (21%)	25 (17%)	3900 (52%)	2522 (51%)	1374 (53%)	2276 (24%)	1440 (21%)	827 (29%)
Use of antenatal corticosteroids not recorded	41 (8%)	25 (8%)	9 (6%)	274 (4%)	194 (4%)	75 (3%)	451 (5%)	349 (5%)	99 (4%)

Columns might not add to 100% because of rounding error. *Does not include 22 women with missing labour status. †Women who delivered preterm after spontaneous onset of labour. ‡Women who delivered preterm after induction of labour or pre-labour delivery (ie, caesarean section). §Does not include 29 women with missing labour status. ¶Does not include 23 women with missing labour status.

Table 1: Use of antenatal corticosteroids in preterm births (n=17 705 deliveries)

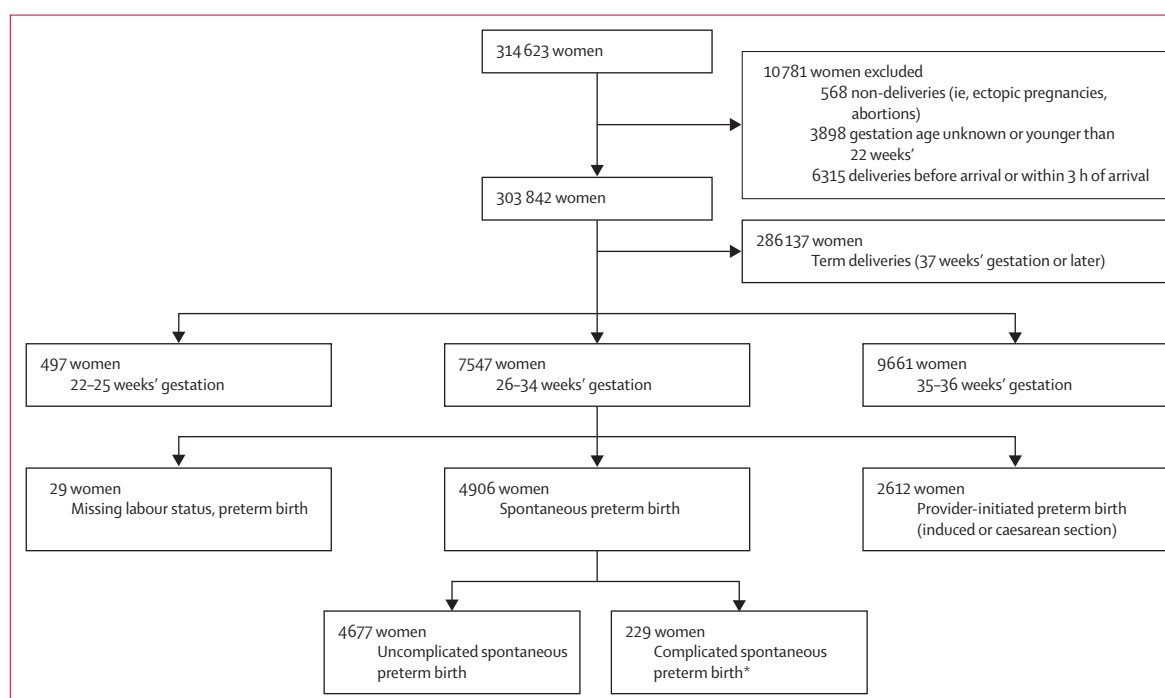


Figure 1: Population profile

*Complicated spontaneous preterm birth includes women who have eclampsia, placental abruption, or sepsis (ie, use of tocolytic drugs is contraindicated).

of bed rest, hydration, or no treatment for preterm labour was also recorded.

Statistical analysis

For our analysis, we included pregnancies at or longer than 22 weeks' gestation and excluded abortions, ectopic pregnancies, and pregnancies with unknown gestational age. We excluded deliveries that occurred before a woman's arrival at the facility or within 3 h of arrival because antenatal corticosteroids and tocolytic drugs would be less applicable in these contexts. Preterm deliveries were stratified into three mutually exclusive groups: 22–25 weeks', 26–34 weeks', and 35–36 weeks' gestation. We established the rate of documented antenatal corticosteroid use, both overall and for each country. We identified women who had spontaneous

preterm labour at 26–34 weeks' gestation and who did not have a major contraindication to tocolysis (ie, eclampsia, placental abruption, or sepsis). We reported on the documented use of tocolysis treatments, with and without antenatal corticosteroids, in these women. We analysed the crude and adjusted associated effect of maternal, neonatal, and facility characteristics on administration of antenatal corticosteroids by using a multilevel logistic regression model. We also reported their individual effects with odds ratios, and adjusted odds ratios and their 95% CIs. Maternal characteristics recorded were age, marital status, education level, parity, mode of delivery, presence of disorders (ie, chronic hypertension, pre-eclampsia or eclampsia, pyelonephritis, influenza-like illness, other infections or sepsis, HIV/AIDS, and malaria and dengue fever), and number

and sex of fetuses. Facility characteristics recorded were location, level of facility, and level of services available.

We used SPSS version 20.0.0 procedure MULTIPLE IMPUTATION to impute missing values for all model variables (see missing rates in table 1). Overall missing rates were 5% or less for all variables, except for years of education (7.7%). Five imputed datasets were created and used in our model. We converted continuous variables (maternal age, years of education, and parity) to categorical variables after imputation for modelling. We also adjusted our model (using SPSS function GENLIMIXED) for clustering due to hierarchical design of the survey (clustering of women within facilities and facilities within countries was accounted for by use of health facilities as sampling units and countries as strata) with random intercepts at the country and facility level. Because of the

weighted sampling design of the WHOMCS, our analysis was self-weighted and no further weighting was applied.

Role of the funding source

JPV, JPS, AMG, MB, and MT are employed by WHO. Some of the funds for the study were from WHO. The non-WHO sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had access to the WHOMCS database. JPV, JPS, and AMG made the decision to submit for publication.

Results

Of 303 842 women included in our analysis, 17705 (6%) gave birth preterm (figure 1). These deliveries occurred across 359 facilities, mainly in secondary (N=94740, 31%)

	Coverage of corticosteroids in all deliveries at 26–34 weeks' gestation			Coverage of both tocolytic drugs and antenatal corticosteroids in uncomplicated, spontaneous deliveries at 26–34 weeks' gestation		
	Women who received drugs (n)	Proportion (%)	95% CI*	Women who received drugs (n)	Proportion (%)	95% CI*
Afghanistan	48 (297)	16%	6.6–34.5	2 (207)	1%	0.2–5.2
Angola	33 (129)	26%	12.2–46.0	2 (79)	3%	0.8–7.6
Argentina	136 (185)	74%	62.9–82.0	52 (88)	59%	46.7–70.5
Brazil	86 (288)	30%	13.9–52.9	14 (105)	13%	8.6–20.1
Cambodia	73 (127)	58%	47.2–67.1	9 (75)	12%	3.7–32.8
China	158 (234)	68%	58.7–75.2	52 (125)	42%	30.0–54.2
Democratic Republic of the Congo	26 (159)	16%	6.8–34.4	9 (131)	7%	1.7–23.6
Ecuador	84 (237)	35%	16.8–59.8	34 (148)	23%	9.7–45.3
India	1021 (1481)	69%	60.8–76.1	140 (1102)	13%	7.5–20.7
Japan	30 (52)	58%	38.2–75.0	12 (22)	55%	28.8–78.1
Jordan	19 (21)	91%	78.0–100	5 (8)	63%	29.0–96.1
Kenya	173 (542)	32%	21.3–44.8	23 (334)	7%	3.0–15.0
Lebanon	43 (76)	57%	41.4–70.6	16 (46)	35%	19.9–53.4
Mexico	300 (558)	54%	38.9–68.0	91 (391)	23%	18.9–28.3
Mongolia	108 (156)	69%	62.8–75.0	17 (55)	31%	23.0–40.1
Nepal	46 (236)	20%	5.7–49.1	0 (187)	0	..
Nicaragua	130 (184)	71%	63.8–76.7	56 (92)	61%	45.0–74.7
Niger	12 (60)	20%	7.5–43.7	2 (42)	5%	1.2–17.4
Nigeria	109 (367)	30%	19.7–42.1	27 (188)	14%	5.9–31.1
Occupied Palestinian territory	22 (25)	88%	75.3–100	4 (4)	100%	..
Pakistan	250 (398)	63%	53.3–71.4	37 (195)	19%	9.6–34.0
Paraguay	68 (99)	69%	60.3–76.0	28 (56)	50%	43.4–56.6
Peru	302 (403)	75%	67.1–81.4	78 (183)	43%	30.9–55.2
Philippines	120 (256)	47%	37.0–57.0	33 (193)	17%	10.5–26.6
Qatar	9 (29)	31%	14.2–47.8	1 (18)	6%	0–16.2
Sri Lanka	287 (439)	65%	56.5–73.3	47 (220)	21%	12.9–33.3
Thailand	108 (244)	44%	34.6–54.3	44 (172)	26%	18.8–33.8
Uganda	41 (154)	27%	19.3–35.5	0 (110)	0%	..
Vietnam	58 (111)	52%	40.6–63.6	13 (101)	13%	5.1–29.1
Total	3900 (7547)	52%	47.5–55.8	848 (4677)	18.1%	15.4–21.2

*95% CIs are adjusted for hierarchical survey design.

Table 2: Coverage of antenatal corticosteroids and tocolytic drugs in countries studied

	Received antenatal corticosteroids (n=3900)	Did not receive antenatal corticosteroids (n=3373)	Odds ratio* (95% CI)	Adjusted odds ratio† (95% CI)
Maternal age				
Younger than 20 years	332 (9%)	437 (13.0%)	0.62 (0.50–0.77)	0.70 (0.57–0.86)
20–35 years	3116 (80%)	2547 (75.5%)	Ref	Ref
Older than 35 years	443 (11%)	379 (11.2%)	0.96 (0.78–1.17)	0.95 (0.76–1.20)
Data missing	9 (<1%)	10 (<1%)	..	..
Marital status				
Married	378 (10%)	391 (12%)	0.82 (0.60–1.11)	1.25 (0.98–1.61)
Not married	3495 (90%)	2950 (88%)	Ref	Ref
Data missing	27 (1%)	32 (1%)	..	..
Years of education				
0 years	573 (15%)	603 (18%)	0.64 (0.41–0.99)	0.84 (0.63–1.11)
1–6 years	576 (15%)	482 (14%)	0.8 (0.60–1.08)	0.83 (0.69–0.99)
7–9 years	723 (19%)	660 (20%)	0.74 (0.55–0.98)	0.87 (0.69–1.10)
10–12 years	1141 (29%)	875 (26%)	0.88 (0.69–1.12)	0.96 (0.80–1.15)
More than 12 years	584 (15%)	392 (12%)	Ref	Ref
Data missing	303 (8%)	361 (11%)	..	..
Parity				
0	1811 (46%)	1448 (43%)	1.06 (0.95–1.19)	1.20 (1.07–1.35)
1–2 children	1580 (41%)	1343 (40%)	Ref	Ref
More than 2 children	508 (13%)	577 (17%)	0.75 (0.61–0.91)	1.04 (0.85–1.27)
Data missing	1 (<1%)	5 (<1%)	..	..
Mode of delivery				
Vaginal delivery	2033 (52%)	2286 (68%)	Ref	Ref
Intrapartum caesarean section	874 (22%)	574 (17%)	1.71 (1.34–2.18)	1.51 (1.13–2.02)
No-labour caesarean section	984 (25%)	488 (15%)	2.27 (1.77–2.90)	2.13 (1.69–2.67)
Data missing	9 (<1%)	25 (1%)	..	..
Maternal disorders				
Chronic hypertension	114 (3%)	64 (2%)	1.56 (1.01–2.41)	1.14 (0.83–1.57)
Pre-eclampsia or eclampsia	714 (18%)	441 (13%)	1.49 (1.22–1.82)	1.14 (0.89–1.46)
Pyelonephritis	23 (1%)	9 (<1%)	2.22 (1.16–4.23)	1.90 (1.07–3.37)
Influenza-like illness	20 (1%)	7 (<1%)	2.25 (1.03–5.98)	1.56 (0.92–2.63)
Other systemic infections or sepsis	85 (2%)	61 (2%)	1.21 (0.81–1.80)	1.28 (0.61–2.69)
HIV/AIDS or HIV wasting syndrome	21 (1%)	28 (1%)	0.65 (0.31–1.37)	1.59 (0.73–3.44)
Malaria or dengue fever	16 (<1%)	27 (1%)	0.51 (0.24–1.11)	0.90 (0.35–2.26)
Sex of infant				
Female	1796 (46.1%)	1592 (47%)	0.93 (0.85–1.03)	0.98 (0.90–1.06)
Male	2096 (53.7%)	1736 (52%)	Ref	Ref
Data missing	8 (0.2%)	45 (1%)	..	..
Number of newborn babies				
One (singleton pregnancy)	3574 (92%)	3153 (94%)	Ref	Ref
Two (twin pregnancy)	296 (8%)	197 (6%)	1.33 (1.08–1.63)	3.59 (1.15–11.24)
Three or more (higher-order multiple pregnancy)	29 (1%)	6 (<1%)	4.26 (1.85–9.84)	1.28 (1.03–1.60)
Missing data	1 (<1%)	17 (1%)	..	..
Location‡				
Urban	3483 (89%)	2762 (82%)	Ref	Ref
Peri-urban	162 (4%)	358 (11%)	0.36 (0.17–0.77)	0.79 (0.58–1.07)
Rural	57 (2%)	96 (3%)	0.47 (0.29–0.77)	0.88 (0.77–1.01)
Data missing	198 (5%)	157 (5%)	..	..

(Table 3 continues on next page)

	Received antenatal corticosteroids (n=3900)	Did not receive antenatal corticosteroids n=3373)	Odds ratio* (95% CI)	Adjusted odds ratio† (95% CI)
(Continued from previous page)				
Level of facility‡				
Primary	52 (1%)	82 (2%)	0.41 (0.22–0.78)	0.79 (0.52–1.22)
Secondary	663 (17%)	969 (29%)	0.45 (0.30–0.66)	0.93 (0.69–1.26)
Tertiary	2677 (69%)	1743 (52%)	Ref	Ref
Other referral level	309 (8%)	383 (11%)	0.53 (0.26–1.05)	1.03 (0.82–1.29)
Data missing	199 (5%)	196 (6%)	..	..

Columns might not add to 100% because of rounding error. 274 women had information missing on receipt of antenatal corticosteroids and are not included. Ref=reference comparator group. *Calculation of crude odds ratios adjusted for clustering due to survey design only. †Multilevel logistic regression model adjusted for maternal characteristics (age, marital status, education, parity, and mode of delivery), maternal disorders (chronic hypertension, pre-eclampsia or eclampsia, pyelonephritis, influenza-like illness, other infections or sepsis, HIV/AIDS, malaria, and dengue fever), infant characteristics (sex and number of fetuses), and facility characteristics (location and level of facility, provision of care free of charge at facility, and level of services available at facility), as well as clustering due to survey design. ‡As reported by head of obstetrics department or facility.

Table 3: Maternal and neonatal infant characteristics associated with use of antenatal corticosteroids at 26–34 weeks' gestation (n=7273)

See Online for appendix

	Number of women (%)
Women receiving drugs for tocolysis	970 (21%)
Calcium-channel blocker only	271 (6%)
Oxytocin antagonist only	26 (1%)
β -agonists only	346 (7%)
NSAIDs or COX inhibitors only	48 (1%)
Magnesium sulphate only	85 (2%)
More than one drug given*	194 (4%)
No drug given; treated with bed rest and hydration only†	1276 (27%)
No treatment given for tocolysis	2248 (48%)
Data missing	183 (4%)

Data for 4677 deliveries. NSAIDs=non-steroidal anti-inflammatory drugs. COX=cyclo-oxygenase. *Use of two or more tocolytic drugs including those listed. †No documented use of any of the named drugs or treatments.

Table 4: Use of tocolytic drugs in women with uncomplicated, spontaneous preterm deliveries at 26–34 weeks' gestation

and tertiary (N=131835, 43%) facilities, with the rest in primary (N=16611, 6%) and other referral level (N=36460 12%) facilities; data were missing for 8.0% (N=24196) of deliveries. The 7547 women who gave birth at 26–34 weeks' gestation accounted for 2.5% of all deliveries. Of these events, 4906 (65%) women had a spontaneous preterm birth, of which 4677 (95%) were spontaneous preterm births without a major contraindication to tocolysis. Table 1 shows data for antenatal corticosteroid use in the 17705 women who delivered preterm; 766 (4%) had data missing for use of antenatal corticosteroids. Of the women who delivered at 26–34 weeks' gestation, 52% received antenatal corticosteroids (table 1).

When stratified by spontaneous preterm birth or provider-initiated preterm birth (ie, induced labour or a pre-labour caesarean section), antenatal corticosteroid use

for women at 26–34 weeks' gestation was similar ($\chi^2=0.62$). When analysed for countries, median antenatal corticosteroid coverage was 54% (range 16–91%, IQR 30–68%; table 2, appendix). Only two countries exceeded 80% use—Jordan (91%) and occupied Palestinian territory (88%)—however, the number of preterm babies in both countries was quite small. Although we did not know the vital status of the fetus at onset of labour, we did a sensitivity analysis by excluding the 1957 women who had stillbirth with signs of maceration (on the assumption that these fetuses were probably not alive at the start of labour). Use of antenatal corticosteroids increased from 52% (n=3900 of 7547) to 56% (n=3836 of 6909) after we excluded these deliveries. Results from the multilevel logistic regression model with multiple imputation (table 3) showed that the adjusted odds of receipt of antenatal corticosteroids were significantly raised in nulliparous women and in both intrapartum caesarean and pre-labour caesarean deliveries. Women with pyelonephritis had raised adjusted odds of antenatal corticosteroid receipt, as did those pregnant with twins and higher-order multiple pregnancies. The adjusted odds of antenatal corticosteroid use were lower in women younger than 20 years and women with 1–6 years of education. The same model without multiple imputation of missing values returned similar results (data not shown), with no change in significance for covariates except for pyelonephritis (not significant in model without multiple imputation; adjusted odds ratio 1.39, 95% CI 0.79–2.43) and influenza (significant in model without multiple imputation; 2.48, 1.56–3.93).

Among the 4677 women with uncomplicated, spontaneous preterm labour who were eligible for tocolytic treatment, almost half received no treatment and a quarter received non-drug treatments (table 4). The most frequently used drugs for tocolysis were β -agonists and calcium-channel blockers. Only 848 (18%) women in this group received a tocolytic drug in

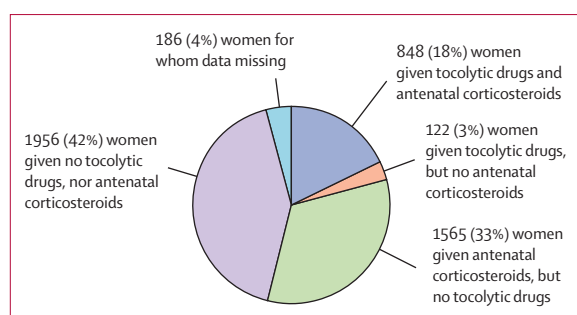


Figure 2: Use of tocolytic drugs, with and without antenatal corticosteroids, in uncomplicated spontaneous preterm births (26–34 weeks' gestation; n=4677)
Tocolytic drugs for preterm labour include calcium-channel blockers, oxytocin antagonists, β -agonists, non-steroidal anti-inflammatory drugs and cyclooxygenase inhibitors, and magnesium sulphate. The no tocolytic drug group indicates women treated with bed rest, hydration, or no treatment for preterm labour.

combination with antenatal corticosteroids (figure 2). Most women received neither a tocolytic drug nor antenatal corticosteroids, or antenatal corticosteroids without a tocolysis drug; and a few received tocolysis without concurrent antenatal corticosteroids. At the country level, rates of tocolytic drug use in combination with antenatal corticosteroids were generally low—median rate was 19% (range 0–100; table 2, appendix).

Discussion

Our analysis showed that antenatal corticosteroids and tocolytic drugs were substantially underused in women in whom they would have been beneficial. Use of antenatal corticosteroids at gestational ages at which benefit is more controversial, or use of tocolytic drugs that are ineffective or have higher rates of adverse outcomes, was common and exposed women and their babies to unnecessary risk. Nearly half of eligible women overall did not receive antenatal corticosteroids, and, in many countries, most eligible women did not receive antenatal corticosteroids. Lower-income countries such as Afghanistan, Democratic Republic of the Congo, Nepal, and Niger have particularly high rates of neonatal mortality¹⁵ and low use of antenatal corticosteroids. Antenatal corticosteroid use in the two high-income countries that we assessed (Japan 56% and Qatar 31%) was surprisingly low; however, this finding must be interpreted cautiously because the number of women (52 and 29, respectively) was quite small. Although there are few reports of antenatal corticosteroid use in low-income and middle-income countries (panel), other investigators have noted similarly wide variations—eg, 4–71% of women received corticosteroids in several Latin American countries^{16–20} and 9–73% of women in four southeast Asian countries.²¹ Of perhaps greater concern is that use of antenatal corticosteroids was low even in preterm births after induction or pre-labour caesarean section; deliveries in which the timing of delivery and need for antenatal corticosteroids could be reasonably anticipated. Although we were unable to

explore specific reasons to explain this finding, it suggests that barriers to poor use of antenatal corticosteroids probably extend beyond poor identification of women at risk of preterm delivery. Almost a quarter of women who delivered at 35–36 weeks' gestation received antenatal corticosteroids despite the fact that perinatal morbidity and mortality benefit at these gestational age intervals is somewhat controversial.² Uncertainty about gestational age is common in low-income and middle-income countries because antenatal care participation and ultrasound availability can be poor—this uncertainty might have contributed to use of antenatal corticosteroids in gestational ages outside of the 26–34 weeks' gestation range. More appropriate prescribing practices could improve outcomes for the 45% of women at 26–34 weeks' gestation who did not receive antenatal corticosteroids.

The use of tocolytics was generally poor, but it is of great concern that more than a third of eligible women received ineffective treatments for preterm labour. No evidence exists to support the use of bed rest²² and hydration (if not dehydrated)²³ to prevent preterm delivery, and magnesium sulphate is not effective to delay birth or prevent preterm birth.²⁴ Haas and colleagues³ did a systematic review and network meta-analysis for drug treatment options to prevent preterm delivery and reported that prostaglandin inhibitors and calcium-channel blockers have the highest probability of improving neonatal outcomes by delaying delivery and have the lowest maternal side-effects. Prostaglandin inhibitor use is complicated by the risk of oligohydramnios and premature closure of the fetal ductus arteriosus.²⁵ Nifedipine is comparatively cheaper,²⁶ is simple to administer, and is the only drug for tocolysis in the WHO Essential Medicines List.²⁷ β -agonists have similar effectiveness to calcium-channel blockers,¹¹ but they have higher rates of maternal adverse effects (such as chest pain, breathing difficulties, heart irregularities, headaches, and shaking). In our analysis, β -agonists were the most commonly used effective tocolytic drug, despite the known maternal side-effects, and only 6% of eligible women received calcium-channel blockers. This pattern might be due to historical reasons; however, it shows that changes in tocolytic prescribing practices could improve both maternal and neonatal outcomes. Ideally, women in spontaneous preterm labour between 26 and 24 weeks of gestation who receive tocolytics should receive antenatal corticosteroids in combination, yet only 15% of eligible women received both treatments and 42% received neither. As far as we know, our data are the first international comparison of tocolytic drug use with antenatal corticosteroids in preterm birth across lower-income countries. Further research on the determinants of tocolytic prescription would help to identify interventions to improve compliance with best practices in preterm labour management.

A 2013 survey by Aleman and colleagues²⁸ identified several barriers to improved uptake of antenatal

Panel: Research in context**Systematic review**

In women at 26–34 weeks' gestation at risk of preterm birth, the efficacy of antenatal corticosteroids to accelerate fetal lung maturation is unquestioned; contributors to a 2006 Cochrane review² explored the subject extensively. Similarly, the efficacy and adverse effects of individual tocolytic drugs (such as betamimetics,¹⁰ calcium-channel blockers,¹¹ oxytocin receptor antagonists,¹² and magnesium sulphate²⁴) have been the subject of Cochrane reviews.

Interpretation

Despite the wealth of trial evidence about the efficacy and indications for antenatal corticosteroids and tocolytic drugs in preterm birth, remarkably little data are available for clinical patterns of their use, particularly in low-income and middle-income countries where most of the global burden of preterm-associated neonatal mortality occurs. Our findings provide the first internationally comparable, comprehensive study of prevalence of use for antenatal corticosteroids. We suggest that a substantial amount of preterm-birth-associated newborn morbidity and mortality could be avoided through improvements in the delivery of these known interventions. Intensive efforts to scale up use of antenatal corticosteroids in facility settings are needed.

corticosteroids in four Latin American countries, including corticosteroids not being available at hospitals and primary health centres, fear or doubt among health providers about side-effects, misinformation about correct use, and insufficient personnel. They also reported economic barriers to access, and fear and misinformation among women about antenatal corticosteroids.²⁸ Although we were unable to identify specific barriers for the use of antenatal corticosteroids and tocolytic drugs, younger women and women with little education were less likely to receive corticosteroids than were others, suggesting social inequalities might be at play.

Our findings have substantial implications for both clinicians and health policy makers. If recognition of preterm labour is to be followed by early antenatal corticosteroids (with or without tocolytic drugs) then drugs should be readily available at the time and place of presentation. We therefore recommend inclusion of dexamethasone or betamethasone or both on national essential medicines lists to improve outcomes for preterm babies. This action would improve access in all health facilities, particularly in lower-level facilities, which are often the point of first contact for women in preterm labour. Additionally, despecialising prescription of antenatal corticosteroids could allow some health professionals (such as emergency doctors and midwives) to give these drugs could reduce delays in access to this life-saving intervention. 2012 WHO guidance for task shifting²⁹ recommends that the use of midwives to give corticosteroids in preterm labour should be researched rigorously.

In facilities where antenatal corticosteroids and tocolytic drug are available but underused or misused, implementation research, including a deeper understanding of barriers to their use, is needed. Clinical guidelines and education for all health-care workers to recognise and manage preterm labour can reduce barriers

to increased use. Interventions to increase demand could also change practice. For example, community mobilisation and provision of antenatal corticosteroids free of charge to all women at risk of preterm labour would not only increase demand, but would also address the socioeconomic inequities in antenatal corticosteroid use and improve coverage in higher-risk subpopulations (such as adolescents and poorly educated mothers).

Some limitations could have affected the results of our analysis. WHOMCS was mainly a study of maternal and perinatal morbidity and mortality, of which preterm birth is an important component, but was not the survey's main aim. The number of countries participating in the multicountry survey was limited by financial constraints; hence, Europe was not sampled. Although robust, the multistage facility sampling design could potentially introduce bias, because women from countries with smaller populations are oversampled compared with women from countries with larger populations. Within the same country, when smaller, lower-level facilities are randomly sampled, complicated deliveries might be under-represented. Conversely, in countries where maternity care is centralised in a few, large facilities (particularly in the capital city) or where such facilities were randomly sampled, complicated deliveries are probably over-represented. These data are probably not representative of smaller facilities and communities not included in the sampling frame; however, we believe it is reasonable to assume that antenatal corticosteroid and tocolytic drug availability is high in large facilities, and that higher-level facilities and coverage rates are probably poorer in lower-level facilities. In some countries, the number of deliveries in lower-level facilities is proportionally greater, thus coverage might still be poor even when the national rate of facility delivery is high. Data for WHOMCS were abstracted from hospital records; in many facilities, these records are suboptimum and use of interventions might not have been documented correctly (particularly those occurring before facility admission). This bias was minimised as much as possible because data collectors consulted with medical staff about missing information; however, some treatment might be undocumented or could have occurred before arrival at the facility, leading to a possible underestimation of coverage. Conversely, failure to recognise preterm births due to poor estimation of gestational age might lead to an overestimate of drug use. Under-recognition of prematurity also probably contributed to the recorded preterm birth rate (5·8%) being lower than was expected based on recent estimates.¹ Fetal status on arrival for delivery, as well as the type, timing, dose, and frequency of antenatal corticosteroids and tocolytic drugs, was not included in WHOMCS, and we were unable to account for all contraindications to these drugs (such as drug allergies, maternal cardiac diseases, and advanced cervical dilatation). A small proportion of antenatal corticosteroid use at 35–36 weeks'

gestation might be attributable to women who were treated earlier than 35 weeks' gestation but who delivered after 35 weeks' during the same admission. Although missing data might have led to a bias in our findings, missing rates were generally low ($\leq 5\%$) and results from modelling, both with and without multiple imputation, were similar, increasing our confidence that missing values had negligible effect.

Despite the evidence for effectiveness of antenatal corticosteroids and tocolytic drugs in preterm deliveries, their use was highly variable and often poor. A substantial proportion of antenatal corticosteroid use was at extremes of gestational age when benefit is controversial, whereas a significant proportion of mothers of infants at 26–34 weeks' gestation did not receive this life-saving intervention. The use of ineffective, less effective, or potentially harmful treatments for tocolysis was also widespread. Implementation research and contextualised health policies are needed to improve drug availability and compliance with best obstetric practices.

Contributors

JPV and JPS conceptualised the Article and analysis plan. JPV did the analyses, in collaboration with JPS and AMG. All authors contributed to the interpretation of results. JPV drafted the initial report and JPS, AMG, RM, PL, ZQ, GC, ML, BF, TG, JZ, MRT, MB, and MT contributed to the content and revisions.

Declaration of interests

We declare no competing interests.

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Obstetric transition in the World Health Organization Multicountry Survey on Maternal and Newborn Health: exploring pathways for maternal mortality reduction

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ABSTRACT

Objective. To test whether the proposed features of the Obstetric Transition Model—a theoretical framework that may explain gradual changes that countries experience as they eliminate avoidable maternal mortality—are observed in a large, multicountry, maternal and perinatal health database; and to discuss the dynamic process of maternal mortality reduction using this model as a theoretical framework.

Methods. This was a secondary analysis of a cross-sectional study by the World Health Organization that collected information on more than 300 000 women who delivered in 359 health facilities in 29 countries in Africa, Asia, Latin America, and the Middle East, during a 2–4-month period in 2010–2011. The ratios of Potentially Life-Threatening Conditions, Severe Maternal Outcomes, Maternal Near Miss, and Maternal Death were estimated and stratified by stages of obstetric transition. The characteristics of each stage are defined.

Results. Data from 314 623 women showed that female fertility, indirectly estimated by parity, was higher in countries at a lower obstetric transition stage, ranging from a mean of 3 children in Stage II to 1.8 children in Stage IV. Medicalization increased with obstetric transition stage. In Stage IV, women had 2.4 times the cesarean deliveries (15.3% in Stage II and 36.7% in Stage IV) and 2.6 times the labor inductions (7.1% in Stage II and 18.8% in Stage IV) as women in Stage II. The mean age of primiparous women also increased with stage. The occurrence of uterine rupture had a decreasing trend, dropping by 5.2 times, from 178 to 34 cases per 100 000 live births, as a country transitioned from Stage II to IV.

Conclusions. This analysis supports the concept of obstetric transition using multicountry data. The Obstetric Transition Model could provide justification for customizing strategies for reducing maternal mortality according to a country's stage in the obstetric transition.

Key words

Women's health; maternal mortality, trends; obstetrics labor complications; maternal welfare, global health; World Health Organization.

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The year 2015 marks the end of the first global cycle of coordinated actions to promote human and social development in the new millennium. This cycle began with the Millennium Declaration in 2000 (1), and since then, the governments of signatory countries, the United Nations and its specialized agencies, civil society, and many partners around the world have set in motion an unprecedented effort to achieve eight broad goals aimed at combatting extreme poverty and promoting human development (2). The Millennium Development Goals (MDG) initiative uses the year 1990 as a baseline, and priorities include improvements in maternal and reproductive health. The fifth goal is to reduce the global maternal mortality ratio (MMR) by 75% from levels observed in 1990, as well as to provide universal access to reproductive health care (2). MMR is a strong social indicator because it can reflect the living conditions of women, the level of population development, and the quality and level of the health system organization (3).

The global MMR showed a significant decline recently, dropping from 380 in 1990 to 210 in 2013, a reduction of approximately 45% (4). Nevertheless, this reduction is still below the original goal. There is a wide disparity among Regions, with MMR ranging from more than 1 000 maternal deaths per 100 000 live births (LB) in some developing countries, to less than 10 per 100 000 LB in others. The estimated risk of a woman dying from causes associated with the pregnancy-postpartum cycle in high-income countries is 1 in 3 400, compared to 1 in 52 in lower-income countries (4).

Despite all the global efforts, 2013 still recorded an estimated 289 000 maternal deaths, an alarming number (4). If this number of deaths were to occur in a single episode, this would easily be recognized as major tragedy. However, since maternal deaths are dispersed and occur mostly in poor and remote settings, often among ethnic minorities, they often go unnoticed by the public and the media. These fatalities have widespread magnitude, directly affecting families, resulting in a loss of structure and stability, and causing a great impact on the community. Sadly enough, the vast majority of maternal deaths could be avoided (3–5).

A secular, worldwide trend towards social development and maternal mor-

talidity reduction has been observed. The trend is more or less visible, depending on the country evaluated. Evolutionary changes in the pattern of MMR reduction, which can occur at a faster or slower pace, are known to be related to the amount and efficiency of government and societal efforts to implement public policies that promote social development and health improvement. This broad pattern includes a shift from maternal deaths predominantly due to direct obstetric causes to deaths due to indirect causes; from deaths due to communicable diseases to deaths caused by non-communicable diseases; from a younger maternal population to an older one; and a decrease in MMR, along with an increase in institutionalized maternity care, and eventually over-medicalization. We have called this phenomenon of gradual changes that countries experience in their pathway towards elimination of avoidable maternal mortality, the “obstetric transition” (6, 7). The proposed stages of obstetric transition are shown in Box 1.

The main objective of this paper was to test whether the proposed features of the Obstetric Transition Model are observed in a large, multicountry, maternal and perinatal health database (8, 9). Secondly, this study aimed to discuss the

dynamic process of maternal mortality reduction using the Obstetric Transition Model as a theoretical framework.

MATERIALS AND METHODS

This was a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health 2010–2012 (WHO MCS); the methodology and details of the primary study are published elsewhere (8, 9). Briefly, the WHO MCS was a cross-sectional study, collecting data from health facilities in 29 countries in Africa, Asia, Latin America, and the Middle East, from May 2010–December 2011.

Participating facilities and individuals

The majority of facilities in this analysis had participated in the previous WHO Global Survey on Maternal and Perinatal Health (10) and were included through a multistage random selection process. In each hospital, data collection took place during a 2–4-month period, depending on the number of annual deliveries in the health facility or group of health facilities selected in each country.

Three groups of women were eligible to participate in the WHO MCS: all those

BOX 1. Stages of the Obstetric Transition

- Stage I (Maternal Mortality Ratio > 1 000 maternal deaths/100 000 live births): the majority of women experiences a situation close to the natural history of pregnancy and childbirth. Stage I is characterized by a very high maternal mortality ratio, with elevated fertility and the predominance of direct causes of maternal mortality, along with a large proportion of deaths attributable to communicable diseases, such as malaria. The majority of women do not receive professional obstetric care or do not have access to health facilities.
- Stage II (Maternal Mortality Ratio: 999 - 300 maternal deaths/100 000 live births): Mortality and fertility remain very high, with a pattern of causes similar to Stage I. However, a greater proportion of women start to seek and receive care in health units.
- Stage III (Maternal Mortality Ratio: 299 - 50 maternal death/100 000 live births): Fertility is variable and direct causes of mortality still predominate. This is a complex stage, because access continues to be an issue for a large part of the population. However, since a high proportion of pregnant women arrive at health services, quality of care is one of the main determinants of health outcomes, particularly related to overburdened health services. Primary prevention, as well as secondary and tertiary prevention, is fundamental to improve maternal health outcomes in this stage. In other words, the quality of care, skilled childbirth care and adequate management of complications are essential for the reduction in maternal mortality.
- Stage IV (MMR < 50 maternal deaths/100 000 live births): maternal mortality is low. There is a low fertility rate and indirect causes of maternal mortality, in particular chronic-degenerative diseases gain increasing importance. An aspect that emerges in this phase is the increasing role of medicalization as a threat to the quality and improvement of health outcomes.
- Stage V (all avoidable maternal deaths are actually prevented; maternal mortality ratio < 5 maternal deaths/100 000 live births). Maternal mortality is very low, the fertility rate is low or very low, and indirect obstetric causes associated with chronic-degenerative disorders are the main causes of maternal mortality. The main challenges in this stage are the consolidation of advances against structural violence (for example, gender inequalities), effective management of vulnerable populations (for example, immigrants, refugees and displaced people in their own country) and sustainability of excellence in quality of care.

Source: References 6 and 7.

admitted for childbirth at one of the selected health units during data collection period; all women with severe maternal outcomes (SMO) classified as cases of maternal near-miss (MNM) associated with childbirth or abortion; and all maternal deaths.

Data collection

The medical charts of all eligible women were reviewed until hospital discharge or until either the 7th day postpartum, abortion, or death, whichever occurred first. WHO criteria (11) were used to identify potentially life-threatening conditions (PLTC) and MNM. Trained data collectors reviewed each chart on daily visits to each health unit facility, recording individual data on pregnancy outcome, severe complications, and clinical management. The paper form used for data collection had been previously pilot-tested. Data was coded and entered into an electronic data management system. Internal consistency and random checks were performed, comparing collected data, hospital records, and electronic data.

Data analysis

The demographic and obstetrics characteristics of all women were described using simple frequencies and percentages. WHO estimates of MMR were used to stratify participating countries into obstetric transition stages. Stage I was not used because none of the participating countries had MMR greater than 1 000 deaths/ 100 000 LB. Stage V was also not used because it was considered a stage where MMR remained uncertain, idealized, and still theoretical (7). The frequency of women with PLTC (i.e., conditions that may lead to a maternal death) and SMO (i.e., MNM and maternal deaths) was calculated according to the stages of obstetric transition.

Due to lack of direct information, some characteristics of obstetric transition were evaluated through proxies. Considering the role of each characteristic in defining the obstetric transition concept, these proxies were selected *a priori*. Parity served as a fertility proxy. The rate of cesarean delivery and labor induction served as proxies for medicalization of care. The frequency and ratio of uterine rupture were used as a proxy for avoidable causes of morbidity and mortality,

since its occurrence is highly preventable by quality intrapartum monitoring and care. Simple frequencies were used to determine the prevalence of conditions selected. The mortality index—the number of maternal deaths divided by the number of women with severe maternal outcomes—was used as an overall indicator of quality of care (6). Subjects with missing data were not excluded and the total number available for each analysis is shown in tables. Statistical analysis was performed using SPSS software, version 21 (SPSS Inc., an IBM company, Chicago, Illinois, United States).

Ethics approval

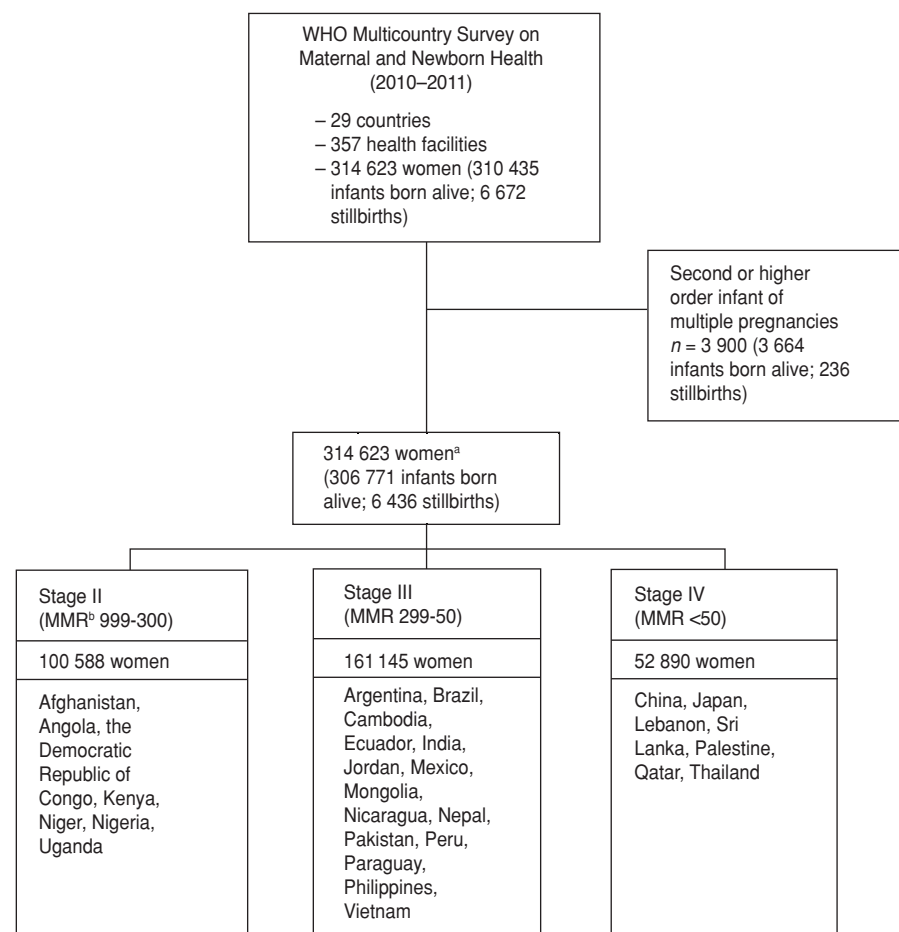
The UNDP/UNFPA/UNICEF/WHO/World Bank Special Program of Research, Development and Research Training in Human Reproduction (HRP) Special-

ist Panel on Epidemiological Research reviewed and approved the protocol of the WHO MCS for technical content. The WHO MCS was approved by the WHO Ethical Review Committee and the relevant ethical clearance mechanisms in all countries (protocol ID: A65661; date of approval: 27 October 2009). Formal authorization for study implementation was obtained from the Ministry of Health of each country, as well as from each participating facility.

RESULTS

Data from 314 623 women admitted for childbirth by 359 health institutions in 29 countries were analyzed. After excluding the second or more newborns from multiple births, there were 306 771 live births and 6 436 still births. Figure 1 presents the analysis flow diagram.

FIGURE 1. The Obstetric Transition Model in the World Health Organization Multicountry Survey (2010–2011): Analysis flow diagram



^a Sum of live births and stillbirths does not equal the number of women because some women had abortions or did not have a delivery.

^b Maternal mortality ratio.

Table 1 presents the demographic and obstetric characteristics of all the study participants. Most of the women (81%) were 20–35 years of age; almost 90% were living with a partner; 57% had 9 years or more of schooling; 88% had never undergone a cesarean section; 77% had a spontaneous labor; 71% had a vaginal delivery; and 42% had no children, while 41% had 1–2 children.

Table 2 presents the frequency of women according to maternal outcome and obstetric transition stage. It was observed that as the obstetric transition stage improved, there was a gradual increase in PLTC (ranging from 70.1/1 000 LB in Stage II to 101.8 in Stage IV), and marked reductions in MNM (ranging from 13.1/1 000 LB in Stage II to 4.2

cases in Stage IV) and maternal death (ranging from 315 deaths/100 000 LB in Stage II to 13 in Stage IV). The mortality index in Stage II was 17.6% (268 deaths/1 525 women with severe maternal outcomes); 16.5% in Stage III (211 deaths/1 278 women); and 3.2% (3 deaths/221 women) in Stage IV.

In the current database, most countries in Stage II are located in Africa, while most in Stage IV are in Asia. All Latin American countries in this database were classified as Stage III, along with other Asian and Eastern Mediterranean countries.

Female fertility, indirectly estimated by parity, was higher in countries at a lower obstetric transition stage, ranging from a mean of 3 children in Stage

II to 1.8 children in Stage IV. The level of medicalization in health facilities in participating countries, defined by the number of cesarean deliveries and number of labor inductions, tended to increase as the stages of obstetric transition increased. In Stage IV, women had 2.4 times more cesarean deliveries (15.3%–36.7%) and 2.6 times more labor inductions (7.1%–18.8%) than women in Stage II. As the stages of obstetric transition increased, the mean age of primiparous women also increased. The occurrence of uterine rupture had a decreasing trend for higher obstetric transition stages. Uterine rupture decreased by 5.2 times and its rate dropped from 178 to 34 cases per 100 000 LB between Stages II and IV (Table 3).

TABLE 1. Demographic and obstetric characteristics of women in the World Health Organization Multicountry Survey on Maternal and Newborn Health (2010–2011) by stages of Obstetric Transition (OT)

Characteristic	All women		OT Stage II		OT Stage III		OT Stage IV	
	No.	%	No.	%	No.	%	No.	%
All women	314 623	100	100 588	32.0	161 145	51.2	52 890	16.8
Age ^a (years)								
< 20	32 328	10.3	11 122	11.1	18 102	11.2	3 104	5.9
20–35	254 307	81.1	79 354	79.4	131 268	81.6	43 685	82.6
> 35	27 054	8.6	9 407	9.4	11 548	7.2	6 099	11.5
Subtotal	313 689	100.0	99 883	100.0	160 918	100.0	52 888	100.0
Marital status ^a								
Without partner	31 693	10.2	11 778	12.0	19 134	11.9	781	1.5
With partner	279 241	89.8	86 366	88.0	141 506	88.1	51 369	98.5
Subtotal	310 934	100.0	98 144	100.0	160 640	100.0	52 150	100.0
Schooling ^a (years)								
< 5	58 630	20.3	35 118	39.8	21 858	14.1	1 654	3.6
5–8	65 718	22.8	22 091	25.0	36 593	23.6	7 034	15.4
9–11	73 611	25.5	9 584	10.9	48 904	31.6	15 123	33.1
> 11	90 816	31.4	21 415	24.3	47 590	30.7	21 811	47.8
Subtotal	288 775	100.0	88 208	100.0	154 945	100.0	45 622	100.0
Number of previous births ^a								
0	132 672	42.3	31 412	31.4	75 510	46.9	25 750	48.7
1–2	130 245	41.5	37 384	37.3	69 324	43.1	23 537	44.5
> 2	51 052	16.3	31 336	31.3	16 117	10.0	3 599	6.8
Subtotal	313 969	100.0	100 132	100.0	160 951	100.0	52 886	100.0
Number of previous cesarean sections ^a								
0	272 302	87.7	90 676	92.8	135 744	85.0	45 882	86.8
1	29 307	9.4	5 282	5.4	18 387	11.5	5 638	10.7
> 1	8 746	2.8	1 804	1.8	5 611	3.5	1 331	2.5
Subtotal	310 355	100.0	97 762	100.0	159 742	100.0	52 851	100.0
Onset of labor ^a								
Spontaneous	241 724	77.3	86 797	87.2	123 228	76.9	31 699	60.0
Induced	32 784	10.5	7 088	7.1	15 757	9.8	9 939	18.8
No labor (cesarean section)	38 073	12.2	5 609	5.6	21 257	13.3	11 207	21.2
Subtotal	312 581	100.0	99 494	100.0	160 242	100.0	52 845	100.0
Mode of delivery ^a								
Vaginal	223 145	71.4	84 050	84.5	105 690	65.9	33 405	63.2
Cesarean section	89 515	28.6	15 421	15.5	54 661	34.1	19 433	36.8
Subtotal	312 660	100.0	99 471	100.0	160 351	100.0	52 838	100.0

^a Pearson Chi-Square test: $P < 0.000$.

TABLE 2. Frequency of women according to maternal outcome with potentially life-threatening conditions and severe maternal outcomes (maternal near miss and maternal deaths) and according to obstetric transition stage, World Health Organization Multicountry Survey on Maternal and Newborn Health (2010–2011)

Country	Obstetric Transition										
	Hospitals	All women	Live births	Potentially life-threatening conditions ^a		Severe maternal outcomes ^a		Maternal near miss cases ^a		Maternal deaths	
	No.	No.	No.	No.	%	No.	%	No.	%	No.	IHMMR ^b
Stage II											
Afghanistan	8	26 148	25 227	923	36.6	440	17.4	421	16.7	19	75
Angola	20	10 450	9 966	587	58.9	92	9.2	57	5.7	35	351
DR Congo	21	8 756	8 395	501	59.7	115	13.7	88	10.5	27	322
Kenya	20	20 354	19 658	1 511	76.9	132	6.7	77	3.9	55	280
Niger	11	11 116	10 714	516	48.2	223	20.8	196	18.3	27	252
Nigeria	21	12 841	11 775	1 701	144.5	371	31.5	298	25.3	73	620
Uganda	21	10 923	10 467	691	66.0	152	14.5	120	11.5	32	306
Subtotal	122	100 588	96 202	6 430	70.1	1 525	16.2	1 257	13.1	268	315
Stage III											
Argentina	14	9 807	9 729	768	78.9	60	6.2	51	5.2	9	93
Brazil	7	7 058	7 019	505	71.9	18	2.6	17	2.4	1	14
Cambodia	5	4 725	4 635	288	62.1	64	13.8	59	12.7	5	108
Ecuador	18	10 245	10 108	1 429	141.4	39	3.9	30	3.0	9	89
Philippines	13	10 783	10 609	830	78.2	41	3.9	29	2.7	12	113
India	21	31 318	30 094	2 214	73.6	283	9.4	174	5.8	109	362
Jordan	1	1 167	1 158	119	102.8	5	4.3	5	4.3	0	0
Mexico	14	13 309	13 167	1 052	79.9	157	11.9	153	11.6	4	30
Mongolia	5	7 365	7 303	823	112.7	62	8.5	61	8.4	1	14
Nepal	8	11 290	10 999	363	33.0	73	6.6	65	5.9	8	73
Nicaragua	8	6 571	6 426	1 707	265.6	125	19.5	119	18.5	6	93
Pakistan	16	13 175	12 729	1 158	91.0	132	10.4	94	7.4	38	299
Peru	16	15 285	15 021	1 116	74.3	175	11.7	169	11.3	6	40
Paraguay	6	3 610	3 595	106	29.5	11	3.1	8	2.2	3	83
Viet Nam	15	15 437	15 411	138	9.0	33	2.1	33	2.1	0	0
Subtotal	167	161 145	158 003	12 616	86.9	1 278	7.8	1 067	6.9	211	94
Stage IV											
China	21	13 277	13 242	927	70.0	34	2.6	34	2.6	0	0
Japan	10	3 537	3 527	655	185.7	21	6.0	21	6.0	0	0
Lebanon	9	4 044	4 008	210	52.4	20	5.0	18	4.5	2	50
Sri Lanka	14	18 129	17 988	862	47.9	76	4.2	73	4.1	3	17
OPT ^c	1	980	975	150	153.8	3	3.1	3	3.1	0	0
Qatar	1	3 950	3 932	509	129.5	14	3.6	14	3.6	0	0
Thailand	12	8 973	8 894	656	73.8	53	6.0	51	5.7	2	22
Subtotal	68	52 890	52 566	3 969	101.8	221	4.3	214	4.2	7	13
Overall	357	314 623	306 771	23 015	86.2	3 024	7.3	2 538	8.0	486	140

^a The prevalence of women with potentially life-threatening conditions, women with severe maternal outcomes and maternal near miss cases are calculated per 1 000 live births.

^b IHMMR: intra-hospital maternal mortality ratio, limited to the first week following pregnancy termination and calculated per 100 000 live births.

^c OPT: Occupied Palestinian Territory.

DISCUSSION

This study applied the obstetric transition concept to examine a large, multi-country database of women who gave birth in health facilities. After country stratification by obstetric transition stage based on country-level MMR estimates (4), we found that as the stages of obstetric transition increased, women tended to have fewer children, have the first child at an older age, and experience increased medicalization of childbirth. The frequency of uterine rupture, used as a proxy for avoidable morbidity and mor-

tality, decreased as the obstetric transition stage increased. The frequency of severe maternal outcomes (both near-miss and mortality) decreased in the study facilities as obstetric transition stage increased.

The Obstetric Transition Model was proposed as a theoretical framework that could provide a particular perspective for examining the dynamic process of maternal mortality reduction. This model allows identification of a country's current obstetric stage, which in turn can indicate which strategies should be used to make further improvements. Because

this model considers specific features of the maternal population (such as fertility, medicalization of pregnancy and childbirth, age of maternal population, and causes of maternal morbidity and mortality), it moves beyond human development index classifications and previous transition models. The features of this model can provide guidance to public health decisionmakers on implementation of appropriate, dynamic, and efficient programs at the global, regional, and national levels (5).

Although the study findings corroborate the hypothesis of an ongoing ob-

TABLE 3. Obstetric transition stages and their characteristics in the World Health Organization Multicountry Survey on Maternal and Newborn Health (2010–2011)

Characteristic	Stage II	Stage III	Stage IV	Overall
All women	100 588	161 145	52 890	314 623
Live births (LB)	96 202	158 003	52 566	306 771
Maternal mortality ^a				
Intra-hospital maternal deaths /100 000 LB	279	134	13	158
Number of maternal deaths	268	211	7	486
Fertility (proxy) ^a				
Parity (± Standard Deviation [SD])	3.0 (±2.2)	2.0 (± 1.3)	1.8 (± 1.1)	2.3 (±1.7)
Medicalization (proxy) ^b				
Cesarean section rate	15.3%	33.9%	36.7%	28.5%
(Number of cesarean sections)	(15 421)	(54 661)	(19 433)	(89 515)
Inductions of labor rate	7.1%	9.8%	18.8%	10.4%
(Number of inductions of labor)	(7 095)	(15 761)	(9 941)	(32 797)
Age of maternal population (proxy) ^a				
Age of nulliparous in years (± SD)	22.3 (± 4.7)	23.4 (± 5.0)	25.8 (± 5.3)	23.6 (±5.1)
Avoidable morbidity & mortality (proxy) ^b				
Ruptured uterus per 100 000 LB	178	80	34	86
Number of ruptured uterus	171	127	18	316

^a $P < 0.000$ (Pearson Chi-Square test).^b $P < 0.000$ (ANOVA).

stetric transition, some aspects deserve further exploration. At first glance, the higher prevalence of potentially life-threatening conditions observed in the more advanced stages of obstetric transition seem counterintuitive. However, this higher prevalence may actually suggest more thorough surveillance and a greater capacity to diagnose pregnancy complications, such as pre-eclampsia, postpartum hemorrhage, and indirect complications. Deaths caused by pre-eclampsia and postpartum hemorrhage are largely preventable, but early diagnosis may be challenging in under-resourced settings. For example, if birth assistants are overwhelmed with patients and lack conditions and resources to offer appropriate care, some cases of mild pre-eclampsia or postpartum hemorrhage may not be detected, leading to a false low PLTC prevalence. In part, this is why we used uterine rupture as a proxy for avoidable causes of maternal deaths: this complication is clearly preventable and rarely overlooked. Although more related to intrapartum care and the ability to detect and manage obstructed labor, we considered uterine rupture a more stable indicator for studying the relationship between obstetric transition stages and the occurrence of preventable causes of maternal mortality. Mortality among cases presenting with severe maternal

outcomes (i.e., the SMO mortality index) could also provide some understanding of the role of quality of care in the obstetric transition (11). Our findings suggest that poor quality of care and difficulties in managing severe complications are a relevant issue at early stages of the obstetric transition.

One of the challenges of maternal mortality reduction is that sustainable and impactful solutions are needed beyond the health sector, and often require an intersectoral approach for health and social development (3, 12–14). In part, this is the reason why the MMR was selected as a development indicator as part of the MDG. Most maternal deaths take place in low-income countries. Reduction requires effective public policies that transcend the health sector. Intersectoral actions, such as health, social, economic, cultural, and environmental policies are needed to induce social development, and result in a global maternal mortality reduction (3, 5, 12–14).

In the health sector, several strategies may be used concurrently to reduce preventable maternal mortality. These include adequate emergency obstetric care; functioning referral systems; available blood transfusion; effective medicines and obstetric surgery; family planning; contraception; high-quality, humane care during pregnancy, child-

birth, and the postpartum period; access to safe abortion; adequate equipment and skilled personnel; and health information and surveillance systems with the appropriate registration of maternal death and near-miss cases and the study of their causes (5).

Although all countries participating in the WHO MCS showed a downward MMR trend in 1990–2013, the highly significant difference in rates between countries highlights the underlying social inequity in the world (4, 9; see [Supplementary material](#) that chart MMR trends by obstetric transition stage). These inequities also occur within countries, where vulnerable populations (i.e., the economically-disadvantaged, those with few years of education, racial and ethnic minorities, refugees, indigenous people) suffer most. These groups and communities suffer the effects of structural violence (e.g., institutionalized racism or sexism that prevent certain people from meeting their basic needs and/or achieving their potential) that can culminate in avoidable death or morbidity (3, 12–14).

We also observed some variation in the obstetric transition status according to the country's geographic location, emphasizing the need to customize strategies. Thus, while in most African countries great emphasis should be di-

rected to strengthening basic social and health infrastructure, in Asia and Latin America further reductions in maternal mortality may be largely dependent on improvements in quality of care. It is important to note that this analysis was conducted at a high level with a lens on certain aspects, however, all aspects remain important and should not be overlooked.

Limitations

This analysis presents both strengths and limitations of note. The size and breadth of the database allowed the obstetric transition concept to be explored on a global scale for the first time. However, the study's cross-sectional design, the source of data (routine medical records), and the ecological approach limited the level of evidence that could be generated. Other limitations include the use of proxies to study some characteristics of the obstetric transition. Also, one must consider that the obstetric transition is the product of complex in-

teractions of social, economic, cultural, biological, and health forces, among others, and that these interactions have implications that go far beyond the health sector.

Conclusions

This analysis supports the theory of obstetric transition using multicountry data. The study findings demonstrated that the Obstetric Transition Model can be used to justify customizing solutions for maternal mortality reduction by aligning with a country's stage in the obstetric transition. Promoting social development and equity, together with health system strengthening and improvements in quality of care, are necessary actions for avoiding maternal deaths that may be more effectively and efficiently applied when a country's stage in the transition is known. Future research could explore population-based data (e.g., demographic health surveys) to further understand the obstetric transition concept.

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Conflicts of interest. None.

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RESUMEN

Transición obstétrica en la Encuesta Global de la Organización Mundial de la Salud sobre Salud Materna y Neonatal: exploración de las vías de reducción de la mortalidad materna

Objetivo. Evaluar si las características propuestas del Modelo de Transición Obstétrica, un marco teórico que puede explicar los cambios graduales que experimentan los países a medida que eliminan la mortalidad materna evitable, se pueden observar en una amplia base de datos de salud materna y perinatal de varios países; y tratar sobre el proceso dinámico de reducción de la mortalidad materna utilizando este modelo como marco teórico.

Métodos. Este estudio consistió en un análisis secundario de un estudio transversal realizado por la Organización Mundial de la Salud que recopiló información sobre más de 300 000 mujeres que dieron a luz en 359 establecimientos de salud de 29 países de África, Asia, América Latina y Oriente Medio, durante un período de 2 a 4 meses en el 2010 y el 2011. Se calcularon los índices de afecciones potencialmente mortales, resultados maternos graves, morbilidad materna extremadamente grave, y muerte materna, y se estratificaron según las etapas de transición obstétrica. Se definen las características de cada etapa.

Resultados. Los datos de 314 623 mujeres indicaron que la fecundidad femenina, calculada indirectamente por el número de partos, fue mayor en los países que se hallaban en las primeras etapas de la transición obstétrica, desde un promedio de 3 hijos en el estadio II a 1,8 en el estadio IV. El nivel de medicalización de los establecimientos de salud de los países participantes, definido por el número de partos por cesárea y el número de partos inducidos, tuvo tendencia a aumentar según avanzaba la etapa de transición obstétrica. En el estadio IV, las mujeres tuvieron 2,4 veces más partos por cesárea (15,3% en el estadio II y 36,7% en el estadio IV) y 2,6 veces más inducciones de parto (7,1% en el estadio II y 18,8% en el estadio IV) que las mujeres en el estadio II. A medida que avanzaban las etapas de transición obstétrica, también se incrementaba la media de edad de las mujeres primíparas. La ocurrencia de rotura uterina mostraba una tendencia descendente, y se reducía 5,2 veces, de 178 a 34 casos por 100 000 nacidos vivos, a medida que un país efectuaba la transición del estadio II al IV.

Conclusiones. Este análisis apoya el concepto de transición obstétrica utilizando datos de varios países. El Modelo de Transición Obstétrica podría justificar la adaptación de las estrategias para reducir la mortalidad materna según la etapa de transición obstétrica en que se halla un país.

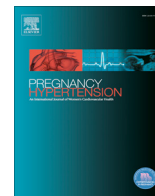
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Salud de la mujer; mortalidad materna, tendencias; complicaciones del trabajo de parto; bienestar materno; salud global; Organización Mundial de la Salud.



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Accuracy of angiogenic biomarkers at ≤ 20 weeks' gestation in predicting the risk of pre-eclampsia: A WHO multicentre study



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ABSTRACT

Objective: To assess the accuracy of angiogenic biomarkers to predict pre-eclampsia.

Design: Prospective multicentre study. From 2006 to 2009, 5121 pregnant women with risk factors for pre-eclampsia (nulliparity, diabetes, previous pre-eclampsia, chronic hypertension) from Argentina, Colombia, Peru, India, Italy, Kenya, Switzerland and Thailand had their serum tested for sFlt-1, PlGF and sEng levels and their urine for PlGF levels at ≤ 20 , 23–27 and 32–35 weeks' gestation (index tests, results blinded from carers). Women were monitored for signs of pre-eclampsia, diagnosed by systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, and proteinuria (protein/creatinine ratio ≥ 0.3 , protein ≥ 1 g/l, or one dipstick measurement $\geq 2+$) appearing after 20 weeks' gestation. Early pre-eclampsia was defined when these signs appeared ≤ 34 weeks' gestation.

Main outcome measure: Pre-eclampsia.

Results: Pre-eclampsia was diagnosed in 198 of 5121 women tested (3.9%) of whom 47 (0.9%) developed it early. The median maternal serum concentrations of index tests were significantly altered in women who subsequently developed pre-eclampsia than in those who did not. However, the area under receiver operating characteristics curve at ≤ 20 weeks' gestation were closer to 0.5 than to 1.0 for all biomarkers both for predicting any pre-eclampsia or at ≤ 34 weeks' gestation. The corresponding sensitivity, specificity and likelihood ratios were poor. Multivariable models combining sEng with clinical features slightly improved the prediction capability.

Conclusions: Angiogenic biomarkers in first half of pregnancy do not perform well enough in predicting the later development of pre-eclampsia.

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1. Introduction

Hypertensive disorders of pregnancy account for approximately 14% of all maternal deaths worldwide [1]. Pre-eclampsia, particularly when presenting early, i.e. ≤ 34 weeks' gestation, is one of

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the leading causes of maternal and perinatal morbidity and mortality [2].

The cause of pre-eclampsia is still unclear, but there is evidence linking its phenotypic expression to levels of the circulating angiogenic and anti-angiogenic factors, placental growth factor (PIGF), soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sEng) [3]. In pre-eclampsia levels of maternal circulating sFlt-1 and sEng are increased and levels of free bioactive PIGF decreased several weeks prior to the onset of signs and symptoms of pre-eclampsia [4–7]. However, when evaluating the predictive ability of these angiogenic factors during early pregnancy, there is dearth of well-designed marker evaluation studies with considerable heterogeneity between protocols [8]. We performed a prospective multicentre study in eight countries to determine the accuracy of PIGF, sFlt-1, sFlt-1/PIGF and sEng levels in serum and PIGF in urine to predict pre-eclampsia in pregnant women considered at risk of developing the disorder.

2. Material and methods

The study was approved by the ethics committees of the participating centers, by the Research Project Review Panel for the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, and by the World Health Organization (WHO) Research Ethics Review Committee.

2.1. Participants

A multicentre prospective observational study was conducted from September 2006 through June 2009 at antenatal clinics in Argentina, Colombia, India, Italy, Kenya, Peru, Switzerland and Thailand. Women were eligible if they were nulliparous or parous with risk factors for pre-eclampsia including diabetes, previous pre-eclampsia, chronic hypertension or under treatment for hypertension, had a gestational age of ≤ 20 weeks at the time of recruitment, and signed an informed consent. Women with known renal disease (except urinary tract infection) or presenting with proteinuria (dipstick $\geq 2+$) were excluded.

Women were evaluated at study entry ≤ 20 weeks' gestation. Testing included collection of maternal venous blood and a single voided urine sample, blood pressure was measured and medical comorbidities were recorded. The tests were repeated at 23–27 and 32–35 weeks' gestation. Routine antenatal care and case management followed the WHO antenatal care model [9], including estimation of gestational age by ultrasound scan or first date of last menstrual period (early ultrasound used universally in Argentina, Italy and Switzerland; in the majority at booking in Colombia and Thailand; only where unsure of dates at booking in Kenya; in approximately half in Peru; and at least once during any stage in pregnancy in India). All samples were analyzed locally. There were no clinical interventions based on the biomarker tests as their results, were unavailable to the attending practitioners. In addition, the technicians measuring the biomarkers' levels were neither aware of the women's health status nor of their diagnoses.

Data were collected at study entry, during antenatal visits, during hospitalizations and at delivery using specifically designed forms and entered into a web-based data management system compliant with the International Conference on Harmonization (ICH) guidelines for good clinical practice (GCP).

2.2. Definitions

Women presenting with a hypertensive disorder were sub classified as: chronic hypertension, gestational hypertension, pre-eclampsia (including superimposed pre-eclampsia, severe pre-

eclampsia and eclampsia). Pre-eclampsia was diagnosed in the presence of hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg) on two occasions at 2 h to one week apart, presenting *de novo* after 20 weeks' gestation, and proteinuria as a protein/creatinine ratio ≥ 0.3 , protein ≥ 1 g/l, or one dipstick measurement $\geq 2+$. Early pre-eclampsia was diagnosed if the disease presented ≤ 34 weeks' gestation, as prior to this landmark expectant maternal management is advocated to minimize prematurity related complications to the baby [10]. Superimposed pre-eclampsia was diagnosed in women with chronic hypertension presenting with proteinuria after mid-pregnancy. The gestational age at which the woman developed pre-eclampsia was when it was first diagnosed regardless of the time of delivery.

2.3. Index test sample collection and immunoassays

Health personnel utilized the sampling handling instructions manual prepared specifically for this study. Maternal samples were collected at study entry (≤ 20 weeks), at 23–27, and 32–35 weeks' gestation. 2 ml of freshly voided urine were rapidly frozen and stored at -70°C and 2 ml of serum from blood obtained by venipuncture were frozen and stored at -70°C . Blood and urine samples were stored in the freezer at each of the centers for a minimum period of eight weeks and a maximum period of twelve weeks before the analyses.

Maternal serum concentrations of sFlt-1, PIGF and sEng as well as urinary concentration of PIGF were determined by commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN, USA) locally at each participating centre. All immunoassays had been validated for serum determinations of the analytes. The intra assay and inter assay coefficients of variation (CV) for sFlt-1 were 3.5% and 8.1%, for PIGF were 5.9% and 10.9% and for sEng were 3.0% and 6.3% respectively. The sensitivity of the assays was: sFlt-1: 5 pg/ml; PIGF: 7 pg/ml; sEng: 7 pg/ml.

Technicians were trained in the putative laboratory methods and provided an assay protocol for guidance. Before the study started, laboratory procedures were standardized and each laboratory was monitored throughout the study to ascertain that the correct standard operating procedures were being followed.

2.4. Sample size and statistical analysis

The incidence of pre-eclampsia is 4% among nulliparous women and up to 20% among women with high risk factors. It is assumed that this last group represents 10% of the pregnant population [11]. This gives an overall prevalence of $(0.04 + 0.20 [0.10]) = 0.06$. Therefore, for the purposes of performing a sample size calculation, it was assumed a prevalence 6% of pre-eclampsia. Considering that a clinically useful test in the first half of pregnancy will have a sensitivity of 80% [12,13] the sample size at 90% power and $\alpha = 0.05$ was estimated to be 12,354.

In 2006–2009, 8703 pregnant women who delivered at a viable gestation were recruited (Fig. S1). Due to a short fall in funding, the samples of 3372 women were not analyzed for angiogenic biomarkers. The study's independent oversight committee instructed us to statistically analyze the data from the remaining 5331 women for publication to avoid delay in dissemination of the findings as the prospect of obtaining results for the remaining samples in near future appeared unlikely. Of the 5331 included women, 210 had no delivery form and were excluded from further analysis.

Participant characteristics were described using mean and standard deviation for continuous variables and percentages for categorical variables. Baseline characteristics comparisons between

the women who had pre-eclampsia and those who had normal pregnancies were performed using Wilcoxon signed-rank test for continuous variables and Fisher Exact test for categorical variables. Characteristics of women excluded due to inability to obtain index test results and those included in the current analysis are shown in Table S1.

The women were included if their delivery form was complete and at least one blood or urine sample had been tested for the index results. The levels were compared between women who did and who did not develop pre-eclampsia. Observations greater than the third quartile plus 1.5 times the interquartile range and less than the first quartile minus 1.5 times the interquartile range were defined as outliers and were excluded [14]. The description of each biomarker was performed transversally within the samples obtained early in pregnancy (≤ 20 weeks), at 23–27, and at 32–35 weeks using median and quartiles due to their asymmetrical distribution. Comparisons of biomarkers between preeclamptic and non preeclamptic women were performed using Wilcoxon signed-rank test.

The predictive accuracy of each biomarker was initially summarized by plotting the estimates of sensitivity (true positive rates) and 1-specificity (false negative rates) in a receiver operating characteristics curve, ROC plot (figures available upon request) [15,16]. The primary analysis for prediction focused on index test results obtained in early pregnancy ≤ 20 weeks' gestation. The area under the ROC curve (AUC) provided information on the performance of the entire range of test results. An AUC of 0.5 describes a non-informative test whereas an AUC of 1.0 represents a test that discriminates perfectly between the presence and absence of disease. The cut-off points considered in the calculations for sensitivity, specificity and likelihood ratios were those pre-specified in the protocol (urinary PIGF <150 pg/ml, ratio sFlt-1/PIGF >5 and sEng >10 ng/ml) based on published literature [7] as well as those that had 90% of sensitivity and 90% of specificity. Serum PIGF and sFlt-1 cut-off points were not pre-specified in the protocol. A positive likelihood ratio >10 and a negative likelihood ratio <0.1 were considered convincing prediction evidence. Moderate prediction can be achieved with positive and negative likelihood ratio values of 5–10 and 0.1–0.2 respectively, whereas those less than 5 and greater than 0.2 yield only minimal prediction [17]. We calculated 95% confidence intervals (CI) to examine uncertainty around the point estimate.

Additional analyses evaluated biomarker testing at 23–27 and at 32–35 weeks' gestation, but these were limited due to a sizable proportion of missing values. In order to be able to assess the performance of the biomarkers at those gestational windows, imputation of missing values was used [18]. The process of imputation was the following: firstly a monotone missing pattern was created using a Markov Chain Monte Carlo (MCMC) method, which assumes multivariate normality, to impute all missing values or just enough missing values to make the imputed data sets have monotone missing patterns. The second step used more specific techniques (for the imputed data set with a monotone missing pattern), depending on the variable. For continuous variables (as it is our case) we checked for normality and then a linear regression was used. Multiple imputation standard errors decrease as the number of imputations increases, it also improves the power and the significance test involving multiple parameters becoming more accurate. Twenty-five imputations are considered sufficient for many realistic situations. Therefore, logistic regression models were built from twenty-five imputed data sets. Results from these models were combined to obtain estimated specificity, sensitivity, likelihood ratios and areas under ROC curves. The predictive accuracy of the index tests for pre-eclampsia or early pre-eclampsia was further evaluated using multivariable logistic regression models. Areas under the ROC curves (AUC) were compared to assess the

incremental value of each biomarker over and above that of clinical features (such as age, body mass index, smoke (yes vs no), pregnancy (multiple vs singleton), hypertension at entry (yes vs no), history of hypertension (yes vs no), treatment for hypertension (yes vs no) using multiple logistic models [19]. Differences between areas were assessed with a 95% CI. If the confidence interval of differences between AUC covers zero indicates that the marker does not improve the prediction achieved with the clinical criteria.

The data analysis for this paper was generated using SAS/STAT® software (Version 9.3).

2.5. Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the study data and had final responsibility for the decision to submit for publication.

3. Results

Index test results at ≤ 20 weeks were available in 99.1% of the 5121 (Argentina 837, Colombia 266, India 1960, Italy 86, Kenya 185, Peru 562, Switzerland 77, Thailand 1148) pregnant women (99% singleton) (Fig. 1). Baseline characteristics (Table 1) comparison showed that women who developed pre-eclampsia had a significant higher body mass index (BMI), higher blood pressure at entry and had higher proportion of parous women affected.

Median gestational age at delivery was 39 weeks (Interquartile range 38–40) for women who did not develop pre-eclampsia and 37 (IQR 35–39) for those developing pre-eclampsia. The prevalence of chronic hypertension, gestational hypertension, pre-eclampsia, and superimposed pre-eclampsia were 2.6% (121/5121), 12.4% (635/5121), 3.5% (177/5121) and 0.4% (21/5121) respectively. Early pre-eclampsia prevalence was 0.9% (47/5121). 11.7% of the women had preterm delivery. Biomarker levels are presented in Fig. 2 and Table 2.

3.1. Predictive performance of index tests in early pregnancy (≤ 20 weeks' gestation)

The median maternal serum concentrations of PIGF, sFlt-1, sFlt-1/PIGF and sEng were significantly different in women who subsequently developed pre-eclampsia than in those who did not (Table 2). However, AUC were closer to 0.5 than to 1.0 for all biomarkers both for predicting pre-eclampsia at any gestation or at ≤ 34 weeks' gestation (Tables 3 and 4). The corresponding sensitivity, specificity and likelihood ratios were poor as well. The prediction achieved with clinical features (age, body mass index, smoke, multiple pregnancy, hypertension or treatment for it) was not particularly augmented by addition of biomarkers except for sEng (Table 5).

3.2. Predictive performance of index tests in late pregnancy (>20 weeks' gestation)

There were a considerable proportion of missing values in this analysis and results of imputed datasets are presented here. At 23–27 weeks' gestation serum PIGF had the highest value of AUC (0.72 and 0.78 for pre-eclampsia at any gestation and that at ≤ 34 weeks' gestation) (Tables 3 and 4). At 32–35 weeks' gestation PIGF had an AUC 0.80 for pre-eclampsia (Table 3). With multivariable models for any pre-eclampsia a slight improvement in prediction was observed when serum sEng, PIGF or sFlt-1/PIGF was added at 23–27 weeks' gestation. An improvement was also

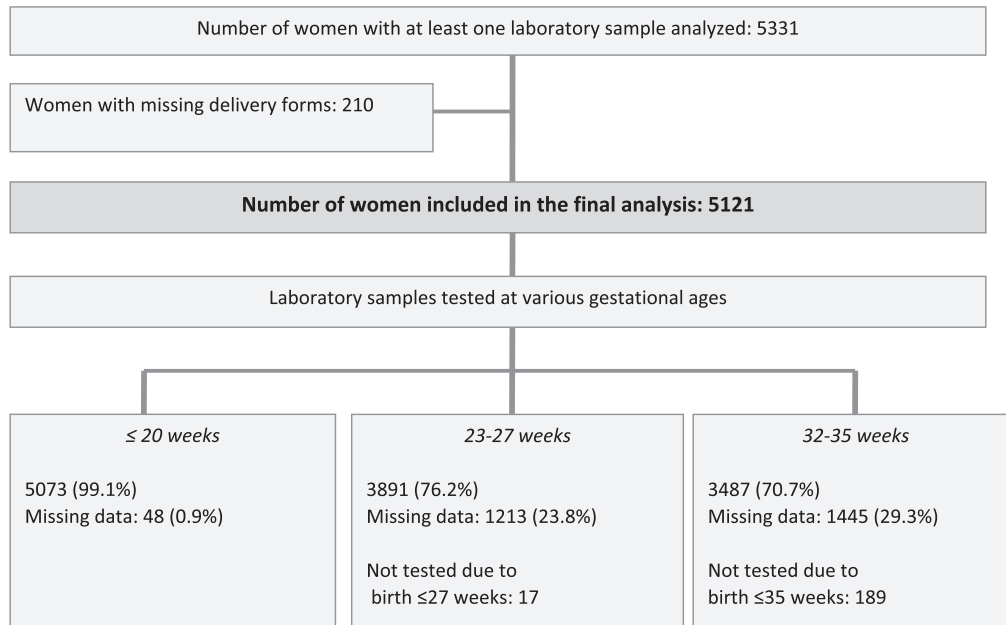


Fig. 1. Flow chart of the study.

Table 1
Baseline characteristics.

Characteristic	Overall (N = 5121)		Preeclampsia status by gestational age							
			No preeclampsia (N = 4923)		Any gestational age (N = 198)		$p^{(1)}$	≤34 weeks (N = 47)		$p^{(1)}$
	Mean	SD	Mean	SD	Mean	SD		Mean	SD	
Age (years)	23.1	5.1	23.0	5.0	24.2	6.4	0.070	25.4	7.3	0.069
Weight (kg)	52.4	12.1	52.1	11.8	59.3	16.6	<0.001	58.5	20.2	0.052
Height (cm)	155.1	7.0	155.1	7.0	155.5	7.5	0.700	154.8	7.1	0.873
BMI	21.7	4.3	21.6	4.2	24.3	5.7	<0.001	24.1	7.0	0.009
GA ⁽³⁾ at entry (weeks)	14.3	4.1	14.4	4.1	14.3	4.0	0.761	15.3	3.6	0.107
	n	%	n	%	n	%	$p^{(2)}$	n	%	$p^{(2)}$
Nulliparous	4830	94.3	4664	94.7	166	83.8	<0.001	38	80.9	<0.001
Smoker	144	2.8	135	2.7	9	4.6	0.126	2	4.3	0.374
Folic acid	2686	51.5	2595	52.7	91	46.0	0.070	30	63.8	0.143
Vitamins/iron	2671	52.2	2594	52.7	77	38.9	<0.001	25	53.2	1.000
Calcium	2170	42.4	2108	42.8	62	31.3	0.001	23	48.9	0.550
Insulin	4	0.0	3	0.1	1	0.5	0.146	1	2.1	0.037
Corticosteroids	3	0.0	3	0.1	0	0.0	1.000	0	0.0	1.000
Aspirin	52	1.0	47	1.0	5	2.5	0.049	2	4.3	0.078
Heparin	2	0.0	2	0.0	0	0.0	1.000	0	0.0	1.000
BP ⁽⁴⁾ ≥ 140/90 (mmHg)	36	0.7	28	0.6	8	4.0	<0.001	3	6.4	0.003
History or Treatment for HTA ⁽⁵⁾	137	2.7	119	2.4	18	9.1	<0.001	6	12.8	0.001

⁽¹⁾ Wilcoxon test.

⁽²⁾ Fisher's Exact test.

⁽³⁾ GA: gestational age.

⁽⁴⁾ BP: blood pressure.

⁽⁵⁾ HTA: hypertension.

observed when any of the markers of 32–35 weeks was added. For early pre-eclampsia, this improvement was observed when adding the information provided by serum sEng and serum PIGF at 23–27 weeks' gestation.

Results of complete case analysis removing missing data are shown in [Tables S2 and S3](#).

4. Discussion

4.1. Main findings

This appears to be one of the largest study designed to examine the predictive accuracy of angiogenic factors for pre-eclampsia.

These results demonstrate that none of the angiogenic and anti-angiogenic biomarker tests at ≤20 weeks' gestation performed well in predicting later development of pre-eclampsia. These results are consistent with other smaller clinical studies demonstrating poor performance of angiogenic factors as predictors of pre-eclampsia [8,20–23]. The combination of biomarkers with clinical characteristics did not substantially improve early prediction. However, we did not have access to maternal uterine artery Dopplers and therefore were unable to evaluate whether addition of this imaging modality would have enhanced our predictive ability as has been demonstrated by other groups [24,25]. Predictive values in second half of pregnancy slightly improved with increasing gestational age and proximity to clinical signs and symptoms.

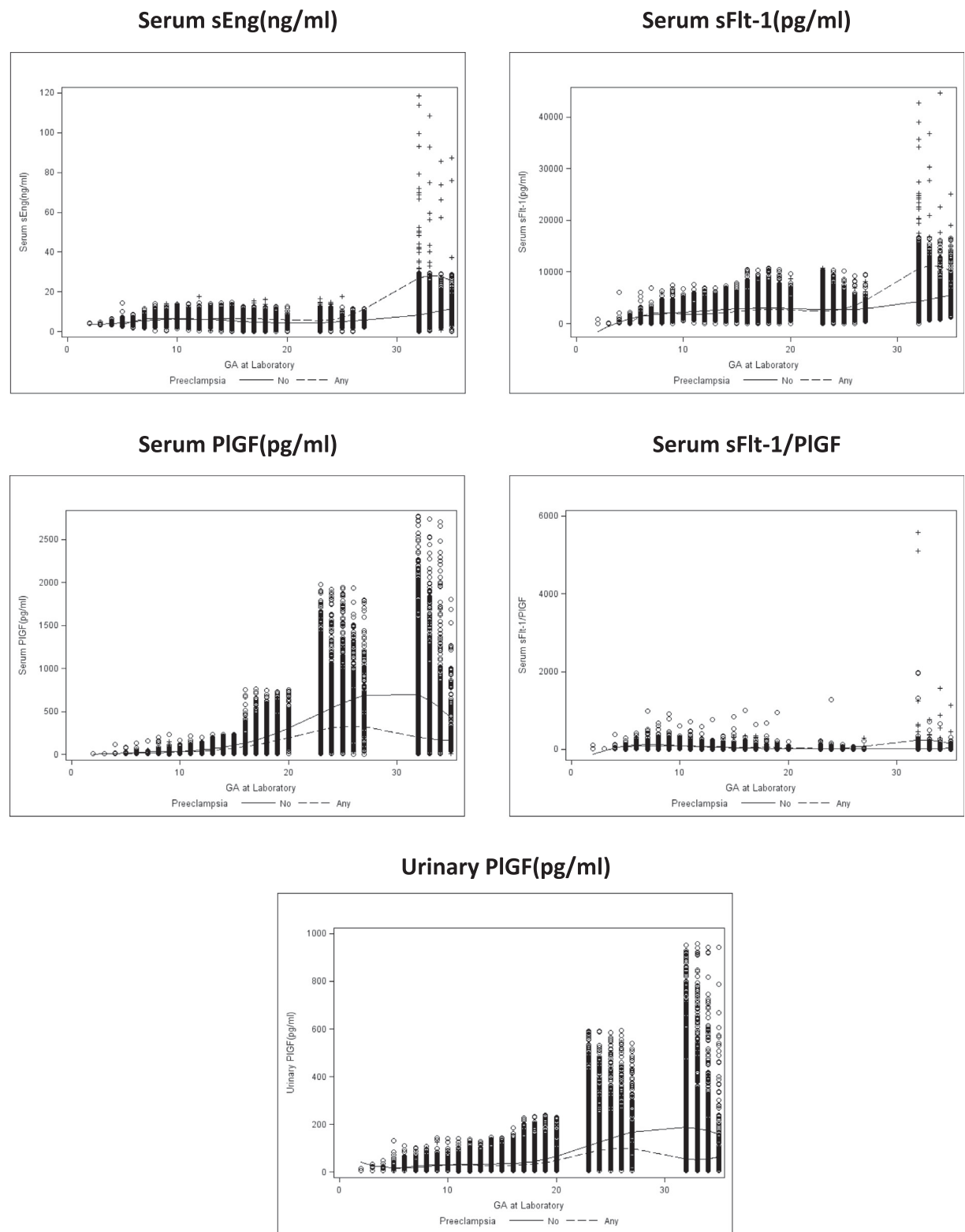


Fig. 2. Distribution of laboratory biomarker values according to gestational age.

4.2. Strengths and limitations

This study complied with quality criteria for well-designed laboratory test evaluations and reported in accordance with STARD (Standard for reporting diagnostic accuracy) [26]. As this was a large, prospective, longitudinal study it was possible to evaluate

a temporal relationship in the behavior of the biomarkers and the onset of the disorder. The study cohort included pregnant women from eight different countries, so our findings are also generalizable. Women were enrolled in the preclinical phase (≤ 20 weeks' gestation), well before the development of preeclampsia. All samples were analyzed within a period of 3 months

Table 2

Cross-sectional analysis by gestational age.

Gestational age	Biomarker	Preeclampsia by gestational age				
		No preeclampsia	Any gestational age	p^*	≤34 weeks	p^*
≤20 weeks	Serum sEng(ng/ml)	5.0 (3.9–6.4)	5.5 (4.3–7.6)	0.0001	5.8 (4.3–8.4)	0.007
	Serum sFlt-1(pg/ml)	2230 (1490–3340)	1890 (1210–2840)	0.0003	2030 (1300–2930)	0.207
	Serum PlGF(pg/ml)	84.6 (35.4–167.8)	55.9 (23.5–117.4)	<0.0001	59.9 (24.8–122.2)	0.041
	Serum sFlt-1/PlGF	27.9 (12.7–62.2)	32.8 (16.1–80.9)	0.0196	30.7 (14.7–81.7)	0.210
	Urinary PlGF(pg/ml)	26.2 (7.3–52.7)	27.0 (7.0–41.8)	0.2871	28.3 (15.9–42.4)	0.812
23–27 weeks	Serum sEng(ng/ml)	4.5 (3.5–5.6)	5.5 (4.2–7.2)	<0.0001	5.4 (4.2–7.1)	0.006
	Serum sFlt-1(pg/ml)	2280 (1480–3580)	2260 (1400–3650)	0.6898	2510 (1460–4310)	0.530
	Serum PlGF(pg/ml)	456.3 (280.5–696.0)	253.7 (122.4–396.0)	<0.0001	153.6 (81.7–356.0)	<0.0001
	Serum sFlt-1/PlGF	5.1 (2.9–9.3)	8.3 (4.3–21.2)	<0.0001	13.4 (4.7–42.5)	<0.0001
	Urinary PlGF(pg/ml)	86.3 (38.4–169.2)	66.4 (27.3–121.2)	0.0017	38.5 (17.3–89.8)	0.001
32–35 weeks	Serum sEng(ng/ml)	7.7 (5.6–11.0)	17.4 (9.8–35.5)	<0.0001		
	Serum sFlt-1(pg/ml)	3760 (2520–5800)	7905 (4750–13,620)	<0.0001		
	Serum PlGF(pg/ml)	513.8 (276.1–894.2)	152.5 (79.0–249.7)	<0.0001		
	Serum sFlt-1/PlGF	6.9 (3.5–16.4)	65.1 (20.5–158.3)	<0.0001		
	Urinary PlGF(pg/ml)	115.6 (43.5–260.9)	36.2 (17.7–79.5)	<0.0001		

Data presented in median (Q1–Q3).

* Wilcoxon test.

Table 3

Ability of biomarkers to predict any preeclampsia analysis based on roc curves.

GA (weeks)	Biomarker	Cut off point	Specificity	Sensitivity	LR(+) CI (95%)	LR(–) CI (95%)	AUC [*]
≤20	Serum sEng (ng/ml)	>3.3	0.2	0.9	1.1 (1.0–1.1)	0.6 (0.4–1.0)	0.58
		>8.1	0.9	0.2	2.2 (1.6–3.0)	0.9 (0.8–0.9)	
		>10.0**	1.0	0.1	2.6 (1.3–5.2)	0.9 (0.9–1.0)	
	Serum sFlt-1 (pg/ml)	>990	0.9	0.2	1.5 (1.0–2.2)	0.9 (0.9–1.0)	0.58
		>3900	0.2	0.9	1.1 (1.0–1.1)	0.6 (0.4–0.9)	
		<17	0.9	0.1	1.1 (0.7–1.6)	1.0 (0.9–1.0)	
	Serum PlGF (pg/ml)	<193	0.2	0.9	1.1 (1.1–1.2)	0.4 (0.3–0.7)	0.59
		<12.7	0.1	0.9	1.0 (1.0–1.1)	0.7 (0.5–1.2)	
		<117	0.9	0.1	1.1 (0.7–1.7)	1.0 (0.9–1.0)	
	Urinary PlGF (pg/ml)	<9.0	0.8	0.2	1.0 (0.8–1.3)	1.0 (0.9–1.1)	0.52
		<77.5	0.2	0.9	1.1 (1.0–1.1)	0.6 (0.4–1.0)	
23–27	Serum sEng (ng/ml)	>3.4	0.2	0.9	1.2 (1.1–1.2)	0.4 (0–0.7)	0.66
		>8.5	0.9	0.3	2.7 (1.7–4.3)	0.8 (0.7–0.9)	
		>10.0**	0.9	0.2	3.6 (1.8–7.2)	0.8 (0.8–0.9)	
	Serum sFlt-1 (pg/ml)	>930	0.1	0.9	1.0 (1.0–1.1)	1.0 (0.6–1.5)	0.52
		>6850	0.9	0.1	1.5 (1.0–2.2)	0.9 (0.9–1.0)	
		<157	0.9	0.3	3.2 (2.2–4.6)	0.8 (0.7–0.8)	
	Serum PlGF (pg/ml)	<650	0.3	0.9	1.3 (1.2–1.4)	0.3 (0.2–0.5)	0.72
		<4.7	0.2	0.9	1.1 (1.0–1.2)	0.6 (0.4–1.0)	
		<5.0**	0.5	0.7	1.4 (0.9–2.2)	0.6 (0.5–0.8)	
	Urinary PlGF (pg/ml)	<28.8	0.9	0.3	2.9 (2.0–4.1)	0.8 (0.7–0.9)	0.60
		<15.1	0.9	0.1	1.5 (1.0–2.2)	0.9 (0.9–1.0)	
		<150.0**	0.3	0.8	1/2 (1.1–1.3)	0.5 (0.4–0.7)	
32–35	Serum sEng (ng/ml)	<193.0	0.2	0.9	1.2 (1.1–1.2)	0.4 (0.3–0.7)	
	Serum sFlt-1 (pg/ml)	>8.3	0.5	0.9	1.8 (1.6–2.0)	0.2 (0.1–0.3)	0.85
		>10.0**	0.6	0.8	2.2 (1.7–2.9)	0.2 (0.2–0.3)	
		>18.3	0.9	0.6	6.4 (3.9–10.3)	0.4 (0.3–0.5)	
	Serum PlGF (pg/ml)	>9100	0.9	0.6	5.5 (3.2–9.5)	0.5 (0.4–0.6)	0.80
		>3180	0.4	0.9	1.4 (1.3–1.6)	0.3 (0.2–0.4)	
		<125	0.9	0.4	4.5 (2.3–8.6)	0.6 (0.5–0.7)	
	Urinary PlGF (pg/ml)	<570	0.5	0.9	1.8 (1.2–2.7)	0.2 (0.1–0.3)	0.80
		<5.0**	0.5	0.9	1.8 (0.8–4.0)	0.3 (0.2–0.5)	
		<135	0.9	0.4	4.0 (2.0–8.0)	0.7 (0.6–0.8)	
	Serum sFlt-1/PlGF	<14.0	0.9	0.3	2.5 (1.7–3.7)	0.8 (0.7–0.9)	0.72
		<233.0	0.4	0.9	1.4 (1.1–1.7)	0.3 (0.2–0.4)	
		<150.0**	0.5	0.8	1.6 (1.4–1.9)	0.4 (0.3–0.5)	

* Area under ROC curve.

** Cut off point established in the study protocol.

after collection, following a standardized methodology. Laboratory technicians were specifically trained in the ELISA technique and monitored during implementation of the study. Although all samples obtained could not be analyzed, a large enough sample size was available that reliably evaluated the predictive ability of angiogenic and anti-angiogenic factors in the first half of preg-

nancy for later development of pre-eclampsia. In this regard, one criticism of our work might be that our study is underpowered because the original sample size was not achieved. This is correct, however it does not automatically imply that power was inadequate because the original assumptions behind prevalence, effect size and significance testing can prove to be outwith what is

Table 4

Ability of biomarkers to predict early preeclampsia analysis based on roc curves.

Gestational age (weeks)	Biomarker	Cut off point	Specificity	Sensitivity	LR(+) CI (95%)	LR(-) CI (95%)	AUC*
≤20	Serum sEng (ng/ml)	>3.2	0.2	0.9	1.1 (1.0–1.2)	0.6 (0.2–1.5)	0.63
		>8.2	0.9	0.3	2.8 (1.5–5.1)	0.8 (0.7–1.0)	
		>10.0**	1.0	0.1	3.4 (1.1–10.6)	0.9 (0.8–1.0)	
	Serum sFlt-1 (pg/ml)	>1600	0.9	0.1	1.2 (0.5–2.9)	1.0 (0.9–1.1)	0.54
		>7900	0.1	0.9	1.0 (0.9–1.1)	1.0 (0.4–2.3)	
	Serum PlGF (pg/ml)	<19	0.9	0.1	0.5 (0.2–1.9)	1.0 (1.0–1.1)	0.60
		<186	0.2	0.9	1.2 (1.1–1.3)	0.4 (0.2–1.0)	
	SerumsFlt-1/PlGF	<5.0**	0.3	0.8	1.1 (0.9–1.3)	0.8 (0.4–1.3)	0.53
		<12.7	0.1	0.9	1.0 (1.0–1.1)	0.8 (0.5–1.2)	
		<118	0.9	0.1	1.1 (0.7–1.7)	1.0 (0.9–1.0)	
	Urinary PlGF (pg/ml)	<17.9	0.9	0.0	0.3 (0.1–1.4)	1.1 (1.0–1.2)	0.50
		<59.6	0.2	0.9	1.1 (1.0–1.2)	0.5 (0.2–1.3)	
		<150.0**	0.1	1.0	1.0 (1.0–1.1)	0.2 (0.0–1.6)	
23–27	Serum sEng (ng/ml)	>3.0	0.2	0.9	1.1 (1.0–1.3)	0.6 (0.2–1.5)	0.63
		>8.8	0.9	0.3	3.0 (1.1–8.5)	0.8 (0.6–1.0)	
		>10.0**	1.0	0.2	4.1 (1.0–17.1)	0.8 (0.7–1.0)	
	Serum sFlt-1 (pg/ml)	>6566	0.9	0.2	1.5 (0.7–3.5)	0.9 (0.8–1.1)	0.53
		>1930	0.1	0.9	1.0 (0.9–1.1)	1.3 (0.3–4.9)	
	Serum PlGF (pg/ml)	<150	0.9	0.5	4.9 (2.5–9.6)	0.6 (0.4–0.8)	0.78
		<566	0.4	0.9	1.5 (1.2–1.9)	0.2 (0.1–0.6)	
	Serum sFlt-1/PlGF	<4.7	0.2	0.9	1.1 (1.0–1.2)	0.6 (0.4–1.0)	0.64
		<5.0**	0.5	0.7	1.4 (0.9–2.2)	0.6 (0.5–0.8)	
		<28.8	0.9	0.3	2.9 (2.0–4.2)	0.8 (0.7–0.9)	
	Urinary PlGF (pg/ml)	<15.4	0.9	0.2	1.8 (0.8–3.7)	0.9 (0.8–1.0)	0.67
		<150.0**	0.3	0.9	1.3 (1.1–1.6)	0.2 (0.1–0.8)	

* Area under ROC curve.

** Cut off point established in the study protocol.

Table 5

Multivariable analysis comparison between areas under roc curves.

Gestational age (weeks)	Biomarker	AUC Model1*	AUC Model2**	Difference between AUC's (95%CI)
A. Any preeclampsia				
≤20	Serum sEng (ng/ml)	0.710	0.735	0.025 (0.001;0.050)
	Serum sFlt-1 (pg/ml)	0.710	0.711	0.002 (–0.008;0.011)
	Serum PlGF (pg/ml)	0.710	0.721	0.011 (–0.003;0.026)
	Serum sFlt-1/PlGF	0.710	0.713	0.003 (0.000;0.007)
	Urinary PlGF (pg/ml)	0.710	0.714	0.004 (–0.006;0.015)
23–27	Serum sEng (ng/ml)	0.710	0.757	0.048 (0.021;0.074)
	Serum sFlt-1 (pg/ml)	0.710	0.713	0.003 (–0.006;0.013)
	Serum PlGF (pg/ml)	0.710	0.766	0.057 (0.025;0.088)
	Serum sFlt-1/PlGF	0.710	0.728	0.018 (0.002;0.034)
	Urinary PlGF (pg/ml)	0.710	0.730	0.020 (–0.003;0.043)
32–35	Serum sEng (ng/ml)	0.706	0.887	0.180 (0.138;0.222)
	Serum sFlt-1 (pg/ml)	0.706	0.855	0.149 (0.108;0.190)
	Serum PlGF (pg/ml)	0.706	0.830	0.124 (0.075;0.172)
	Serum sFlt-1/PlGF	0.706	0.808	0.101 (0.066;0.137)
	Urinary PlGF (pg/ml)	0.706	0.784	0.020 (0.037;0.118)
B. Early preeclampsia				
≤20	Serum sEng (ng/ml)	0.737	0.780	0.042 (–0.004;0.088)
	Serum sFlt-1 (pg/ml)	0.737	0.738	0.001 (–0.027;0.028)
	Serum PlGF (pg/ml)	0.737	0.757	0.020 (–0.021;0.060)
	Serum sFlt-1/PlGF	0.737	0.746	0.009 (–0.005;0.023)
	Urinary PlGF (pg/ml)	0.737	0.743	0.006 (–0.017;0.029)
23–27	Serum sEng (ng/ml)	0.737	0.781	0.044 (0.001;0.088)
	Serum sFlt-1 (pg/ml)	0.737	0.743	0.005 (–0.007;0.018)
	Serum PlGF (pg/ml)	0.737	0.823	0.086 (0.015;0.157)
	Serum sFlt-1/PlGF	0.737	0.764	0.027 (–0.003;0.058)
	Urinary PlGF (pg/ml)	0.737	0.782	0.044 (–0.006;0.095)

* AUC Model1: area under ROC curve · Model with the following covariates: age, body mass index, smoke (yes vs no), pregnancy (multiple vs singleton), hypertension at entry (yes vs no), history of hypertension (yes vs no), treatment for hypertension (yes vs no).

** AUC Model2: area under ROC curve · Model with covariates in Model1 plus the biomarker.

observed. In this situation the power estimations loose relevance. The ultimate purpose of a sizable study is to produce a reliable result, i.e. a precise result. It is confidence interval that is most informative in assessing reliability of estimation [27]. In our case

the observed point estimates of accuracy and the width of confidence interval around them make clear that our findings are reliable. For example, when LR+ is 1.1 (0.7–1.7) and LR– 1.0 (0.9–1.0) for serum sFlt-1/PlGF at ≤20 weeks' gestation for

predicting pre-eclampsia (Table 4), there is hardly anything to be gained by seeking greater numbers. Thus, our negative findings merit consideration.

Our study had some limitations. Early onset pre-eclampsia was noted in only 47 subjects out of the 5121 open tested. This raises the possibility that a type II error due to lack of power may have accounted for the negative results with respect to early onset pre-eclampsia in our study. Furthermore, despite the large number of women participating in the study, only a proportion (5121/8703 women) had index test results available for analysis. However, these women had baseline characteristics similar to those without index test results. Our study utilized the conventional first generation manual ELISA assay method for measuring biomarkers as at the time of this study no automated assays were available. In order to decrease the operator fallibility, much time and effort were invested in training technicians and standardizing laboratories across the participating countries. Finally, there may have been errors in gestational age as we did not have early ultrasound dating in all the participants. This deficiency may affect our inferences concerning early onset pre-eclampsia, but it is unlikely to impact on our inferences concerning prediction of any pre-eclampsia.

4.3. Interpretation

Our study has important implications in the understanding of the pathogenesis of pre-eclampsia. Although median levels of angiogenic factors were significantly altered in the pre-eclampsia group, AUC results were relatively modest in their prediction capacity. One explanation may be that the clinical definition of pre-eclampsia is imperfect and includes a heterogeneous mixture of patients with other disorders that mimic pre-eclampsia (for example obesity with hypertension and proteinuria, the latter due to glomerulomegaly). In fact one study monitored by renal biopsy found the diagnosis of pre-eclampsia erroneous in approximately 15% of nulliparas and in more than 40% of multiparas [20]. Of further interest is a recent report that shows that angiogenic factors are particularly altered only in a subgroup of patients who have multi-systemic features of pre-eclampsia and adverse maternal and neonatal outcomes suggesting that angiogenic factors might identify those patients who require the most vigilant observation [28–30]. It is also possible that angiogenic factors are only altered in a subset of preeclampsia and that other pathways may be altered in non-angiogenic forms of pre-eclampsia. Future studies are needed to carefully subtype pre-eclampsia characterized by angiogenic imbalance from other hypertensive disorders of pregnancy that may have different etiologies [31]. In addition, it is important to be aware the associations, even if considered causal, do not always translate into accurate predictions. In test evaluation, we examine whether test results can usefully discriminate between those who will and those who will not develop disease [32]. To be a good index tests, biomarkers will have to demonstrate associations with pre-eclampsia large in magnitude.

5. Conclusion

Angiogenic biomarker tests performed at ≤ 20 weeks' gestation do not perform well enough in predicting pre-eclampsia for incorporation into current practice.

Disclosure of interests

SAK is a co-inventor on patents on pre-eclampsia biomarkers held by the Beth Israel Deaconess Medical Center, Boston. SAK has served as a consultant to Siemens Diagnostics, Roche, has

financial interest in Aggamin Therapeutics and has received research funding from ThermoFisher Scientific.

Contribution to authorship

MW, SAK, MDL, ACA and GC conceived and designed the study. MW, CC, ACA, GC, SF, SAK, OL, PL, ES, NZ, TF, AMG, MDL participated in the trial implementation. CC was responsible for data analysis, and MW, KK, and CC interpreted the data. MW, KK, and CC drafted the report with input and editing from all authors.

Details of ethics approval

The study was approved by the ethics committees of the participating centers, by the Research Project Review Panel for the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, and by the World Health Organization (WHO) Research Ethics Review Committee.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.preghy.2015.09.004>.

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Clinical pharmacokinetic properties of magnesium sulphate in women with pre-eclampsia and eclampsia: a systematic review

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Background The pharmacokinetic basis of magnesium sulphate (MgSO₄) dosing regimens for eclampsia prophylaxis and treatment is not clearly established.

Objectives To review available data on clinical pharmacokinetic properties of MgSO₄ when used for women with pre-eclampsia and/or eclampsia.

Search strategy MEDLINE, EMBASE, CINAHL, POPLINE, Global Health Library and reference lists of eligible studies.

Selection criteria All study types investigating pharmacokinetic properties of MgSO₄ in women with pre-eclampsia and/or eclampsia.

Data collection and analysis Two authors extracted data on basic pharmacokinetic parameters reflecting the different aspects of absorption, bioavailability, distribution and excretion of MgSO₄ according to identified dosing regimens.

Main results Twenty-eight studies investigating pharmacokinetic properties of 17 MgSO₄ regimens met our inclusion criteria. Most women (91.5%) in the studies had pre-eclampsia. Baseline serum magnesium concentrations were consistently <1 mmol/l across studies. Intravenous loading dose between 4 and 6 g was associated with a doubling of this baseline concentration half an hour after injection. Maintenance infusion of 1 g/hour

consistently produced concentrations well below 2 mmol/l, whereas maintenance infusion at 2 g/hour and the Pritchard intramuscular regimen had higher but inconsistent probability of producing concentrations between 2 and 3 mmol/l. Volume of distribution of magnesium varied (13.65–49.00 l) but the plasma clearance was fairly similar (4.28–5.00 l/hour) across populations.

Conclusion The profiles of Zuspan and Pritchard regimens indicate that the minimum effective serum magnesium concentration for eclampsia prophylaxis is lower than the generally accepted level. Exposure–response studies to identify effective alternative dosing regimens should target concentrations achievable by these standard regimens.

Keywords Eclampsia, magnesium sulphate, pharmacokinetics, pre-eclampsia, serum magnesium.

Tweetable abstract Minimum effective serum magnesium concentration for eclampsia prophylaxis is lower than the generally accepted therapeutic level.

Linked article This article is commented on by FG Cunningham and DB Nelson. To view this mini commentary visit <http://dx.doi.org/10.1111/1471-0528.13776>.

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Introduction

Magnesium sulphate (MgSO_4) has been used to treat pre-eclampsia and eclampsia for more than a century and is currently the anticonvulsant of choice for the prevention and control of eclamptic fits.^{1,2} Historically, the total dose of MgSO_4 used for treating pre-eclampsia and eclampsia was gradually increased from as low as 2 g/24 hours to as high as 54 g/24 hours with the belief that this would increase clinical efficacy.^{3–5} All these studies reported good control of convulsions despite the considerable variations in the regimen, route of administration and total dose of MgSO_4 used. The mechanism of action of MgSO_4 in eclampsia prophylaxis and treatment remains poorly understood and to date, there has been no rigorous evaluation of therapeutic serum magnesium concentration for preventing or treating eclamptic seizures. The so-called minimum therapeutic level of 2 mmol/l has been suggested based on clinical and laboratory observations in earlier studies rather than standard exposure–response studies.^{3,6}

The lack of knowledge on how MgSO_4 works is supported by reports of clinical efficacy among pre-eclamptic women with lower serum magnesium levels, and clinical failure among those with serum magnesium levels within the generally accepted therapeutic range.^{7,8} The two currently recommended regimens (Zuspan and Pritchard) have been internationally accepted as standard regimens on the basis of their proven clinical efficacy in the two largest MgSO_4 trials.^{1,2} Although these trials showed comparable clinical efficacy for the predominantly intramuscular (Pritchard) and intravenous (Zuspan) regimens, they also highlighted the lack of understanding of the minimum effective dose for eclampsia prevention and treatment.

More recently, concerns about adverse events with the use of standard regimens, and coverage limitations posed by health resource requirements in low-income settings⁹ have renewed interest in identifying the minimum effective dose of MgSO_4 for preventing and treating eclampsia. In response, WHO has embarked on a research project to identify a simpler MgSO_4 regimen based on the minimum dose required to achieve clinical efficacy. An initial step of this effort requires a comprehensive review of pharmacokinetic data that are available for MgSO_4 , which along with the related efficacy data will help to establish the serum magnesium levels that should be targeted in standard exposure–response studies. The aim of this study was to systematically review available data on clinical pharmacokinetic properties of MgSO_4 when used for the treatment of pre-eclampsia and eclampsia.

Methods

We prepared this review in accordance with PRISMA guidelines and followed a protocol. Eligible studies included observational and experimental studies where MgSO_4 was used for eclampsia prophylaxis and/or treatment, and a complete or partial pharmacokinetic profile of MgSO_4 was reported, irrespective of the routes and duration of administration or dosage regimen. Participants were women who received MgSO_4 for the prevention or treatment of eclampsia, regardless of their gestational age at treatment or pregnancy outcomes. We did not impose any restrictions based on the number of participants involved in the study. For the purpose of this review, where a study had another arm of women who were not pregnant, had a normal pregnancy, or received MgSO_4 for reasons other than pre-eclampsia and eclampsia, we only extracted data for women with pre-eclampsia and eclampsia. Where such data disaggregation and extraction were impossible, we excluded the study from the review.

The outcomes of interest consisted of basic pharmacokinetic parameters reflecting the different aspects of absorption, bioavailability, distribution and excretion according to the various dosing regimens identified. These included baseline, peak and steady-state serum magnesium concentrations through the period of drug administration, percentage ionised magnesium (Mg^{2+}), volume of distribution, central nervous system and fetal distribution, plasma renal clearance, half-life, and serum concentrations associated with toxic side effects.

We searched MEDLINE, CINAHL, POPLINE, and Global Health Library in October and November 2013 and updated the search in March 2015. The detailed search strategies are included in Table 1. We also searched the reference lists of all eligible studies. No language or date restrictions were applied.

BOO and OTO independently assessed the initial search outputs for potentially eligible studies. BOO and QL assessed the search outputs in the updated search. BOO and OTO independently extracted data using a standardised data form. Any discrepancies were resolved through discussion and consensus between the two authors. We included data from studies that combined women with pre-eclampsia and eclampsia where it was impossible to disaggregate the data accordingly. Where possible, we separately extracted data for women with pre-eclampsia and eclampsia.

Given the significant methodological heterogeneity, variations in reporting format and sparseness of pharmacokinetic data among studies reporting on the same dosage regimen, the available pharmacokinetic parameters for each MgSO_4 regimen identified were qualitatively synthesised according to the two predominant routes of administration

Table 1. Search strategies

Electronic databases				
MEDLINE	POPLINE	GLOBAL HEALTH LIBRARY	CINAHL	EMBASE
'Magnesium Sulfate'[Mesh] OR 'Magnesium Sulfate' OR 'Magnesium Sulphate' OR 'MgSO4' OR '7487-88-9' [RN] OR 'mg longoral' OR 'sulfamag' OR sulmetin OR sulmetine AND 'Hypertension, Pregnancy-Induced'[Mesh] OR 'Pregnancy Toxemias'[Mesh] OR 'pre-eclampsia' OR 'preeclampsia' OR 'pregnancy toxemia' OR 'pregnancy toxemias' OR 'eclampsia' OR 'eclampsias'	(magnesium sulfate) OR (magnesium sulphate)	[(magnesium sulfate) OR (magnesium sulphate)] AND [(pre-eclampsia) OR (preeclampsia) OR (eclampsia) OR (eclampsias)]	TX 'gestational hypertension' OR TX 'hypertension in pregnancy' OR TX 'maternal hypertension' OR TX 'pregnancy hypertension' OR TX 'pregnancy induced hypertension' OR TX 'maternal hypertension' OR TX 'pregnancy toxemia' OR TX 'eclamptic toxemia' OR TX 'eclamptogenic toxemia' OR TX 'EPH gestosis' OR TX 'eph syndrome' OR TX 'gestational toxemia' OR TX 'gestational toxicosis' OR TX 'gestosis' OR TX 'gestosis, eph' OR TX 'hep syndrome' OR TX 'pregnancy toxemia' OR TX 'pregnancy toxemias' OR TX 'pregnancy toxicosis' OR TX 'toxemia gravidum' OR TX 'toxemic pregnancy' OR TX 'toxicosis gravidarum' OR TX 'pre eclampsia' OR TX 'pre eclamptic toxemia' OR TX 'pre eclamptic toxemia' OR TX 'preeclampsia' OR TX 'preeclamptic toxemia' OR TX 'preeclamptic toxemia' OR TX 'puerperal tetany' OR TX 'eclampsia' OR TX 'eclampsias' OR (MH 'Pregnancy-Induced Hypertension+') OR (MH 'Eclampsia+') OR (MH 'Pre-Eclampsia+') AND (MH 'Magnesium Sulfate') OR TX 'magnesium sulfate' OR TX 'magnesium sulfate' OR TX 'MgSO4' OR TX '7487-88-9' OR TX 'mg longoral' OR TX 'sulfamag' OR TX sulmetin OR TX sulmetine OR TX 'Magnesium sulphate'	'gestational hypertension' OR 'hypertension in pregnancy' OR 'maternal hypertension' OR 'pregnancy hypertension' OR 'pregnancy induced hypertension' OR 'maternal hypertension'/exp OR 'pregnancy toxemia'/exp OR 'eclamptic toxemia' OR 'eclamptogenic toxemia' OR 'EPH gestosis' OR 'eph syndrome' OR 'gestational toxemia' OR 'gestational toxicosis' OR 'gestosis' OR 'gestosis, eph' OR 'hep syndrome' OR 'pregnancy toxemia' OR 'pregnancy toxemias' OR 'pregnancy toxicosis' OR 'toxemia gravidum' OR 'toxemic pregnancy' OR 'toxicosis gravidarum' OR 'eclampsia and preeclampsia'/exp OR 'pre-eclampsia' OR 'pre-eclamptic toxemia' OR 'pre-eclamptic toxemia' OR 'pre eclampsia' OR 'preeclampsia' OR 'preeclamptic toxemia' OR 'puerperal tetany' OR 'eclampsia' OR 'eclampsias' AND 'magnesium sulfate'/exp OR 'magnesium sulfate' OR mgso4 OR '7487-88-9':rn OR 'mg longoral' OR 'sulfamag' OR sulmetin OR sulmetine OR 'magnesium sulfate'/de OR 'Magnesium sulphate' AND NOT ['animal'/exp NOT ('animal'/exp AND 'human'/exp)]

—intravenous and intramuscular. Findings were presented as continuous data with measures of central tendency and distribution as reported by the original authors.

For the purpose of this review, we expressed all magnesium levels in the standard international (SI) units [millimole/litre (mmol/l)] by applying standard conversion factors as appropriate. To convert to mmol/l, the reported serum magnesium values in milligram/decilitre (mg/dl) and milliequivalent/litre (mEq/l) were multiplied by 0.411 and 0.500, respectively.¹⁰

We designed a checklist and criteria for quality assessment based on a modification of the QUADAS-2 tool¹¹ (Table S1). The checklist has eight domains: adequacy of

sample size for reliable pharmacokinetic study; representativeness of involved participants to population of interest; adequate reporting of co-variables; study primary objective; reporting of details of laboratory methods used; relevance of laboratory method to contemporary practice; reporting of baseline magnesium level; and duration of follow-up and attrition bias. We considered the overall risk of bias of a study to be 'low' when four or more of the above listed domains were assessed to be at low risk of bias; 'uncertain' when the risk of bias was unclear in five or more domains, or in four domains but with high risk of bias in any of the remaining domains; and 'high' when the risk of bias was assessed as high in three or more domains.

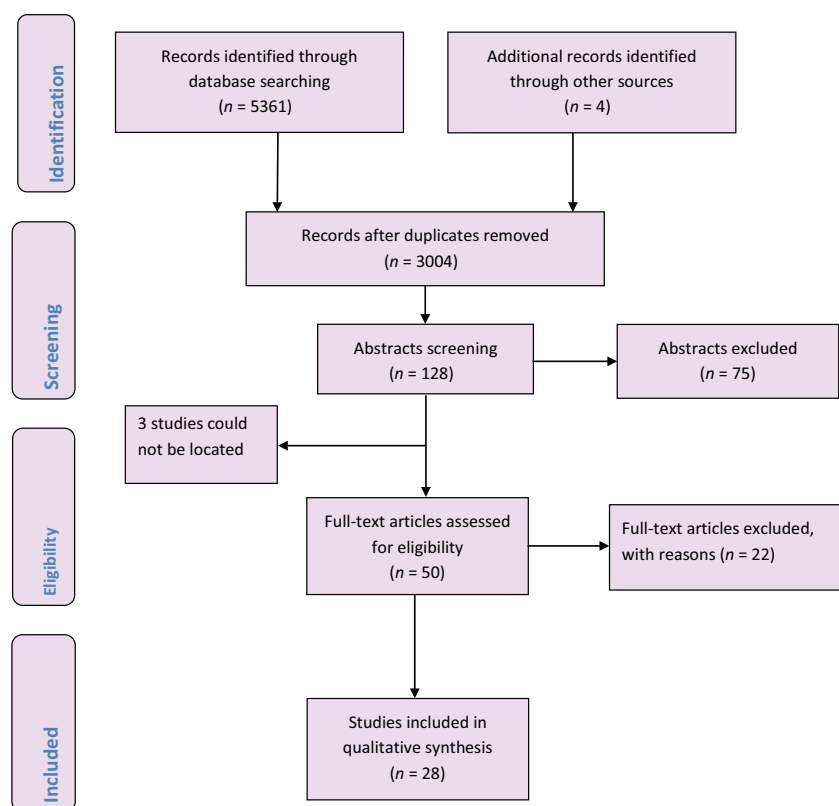


Figure 1. Detailed data selection process.

Results

The search strategies yielded 5361 citations from the electronic databases and four additional citations from other sources. Fifty-three potentially eligible studies were identified after screening of titles and abstracts and removal of duplicates (Figure 1). Full texts of 50 of these 53 studies (three could not be located) were retrieved and assessed. Twenty-eight studies published over a span of seven decades and conducted in the Americas, Europe, Asia, and sub-Saharan Africa met the inclusion criteria.^{3,5,8,12–36} The studies involved a total of 1466 women with pre-eclampsia and/or eclampsia. The majority (91.5%) of these women received MgSO₄ for the treatment of pre-eclampsia and a smaller proportion (8.5%) received the drug for treatment of eclampsia. The study designs were cross-sectional, case-control, randomised and non-randomised trials. Four of the studies used model-based techniques to determine pharmacokinetic parameters (see characteristics of included studies in Table S2). Twenty-two studies were excluded from this review for various reasons (see list of excluded studies in Box S1 and their characteristics in Table S3). Overall, the included studies were very heterogeneous mainly in relation to how blood samples were col-

lected, the timing of serum magnesium estimation, storage method prior to laboratory investigation and laboratory techniques used to estimate magnesium levels.

Table S4 and Figures S1–S3 present the risk of bias assessment for all domains across the included studies, according to the various intravenous and intramuscular regimens identified. Overall, 12 studies were assessed to be at low risk of bias,^{5,8,17–19,22,26,28,29,32,33,35} 13 at uncertain risk of bias^{3,12–16,20,24,25,27,30,34,36} and 3 at high risk of bias.^{21,23,31} For 23 studies that examined intravenous regimens, 10 were assessed to be at low risk of bias^{5,8,17–19,22,26,32,33,35}, 11 at uncertain risk of bias^{3,12–14,16,24,25,27,30,34,36} and two at high risk of bias.^{21,23} For the nine studies that examined only intramuscular regimens, three studies were assessed to be at low risk of bias^{5,28,29} five at uncertain risk of bias^{3,15,16,20,30} and one at high risk of bias.³¹

Intravenous regimens

4-g loading dose and 1 g/hour continuous maintenance infusion (Zuspan regimen)

Seven studies reported pharmacokinetic data based on the Zuspan regimen.^{5,12,17,18,24,27,33} The reported baseline levels

Table 2. Serum magnesium concentration-time profile for intravenous regimens

Regimen	Study	n	Mean serum magnesium in mmol/l (SD)								
			Baseline	½ hour	1 hour	2 hours	4 hours	8 hours	12 hours	24 hours	Steady state
4-g loading + 1 g/hours continuous maintenance	Abbade et al. ^{12,****}	15	0.74 (0.04)	1.48 (0.16)	1.44 (0.16)	1.36 (0.21)	1.36 (0.21)	—	—	—	
	Cruikshank et al. ^{18,****}	20	0.74 (0.03)	—	—	—	—	—	1.70*	—	
	Manorot et al. ^{24,****}	25	—	1.70 (0.25)	1.62 (0.30)	1.60 (0.23)	1.55 (0.15)	—	—	—	
	Sibai et al. ^{5,****}	7	—	—	1.31	1.31	1.44	1.48	1.56	1.64	
	Tongsong et al. ^{33,****}	24	—	—	—	1.75	1.76	—	—	—	
	Chuan et al. ^{17*,****}	116	0.81	—	—	—	—	—	—	1.70**	
	Salinger et al. ^{27*,****}	153	0.85	—	—	—	—	—	—	—	
4-g loading + 2 g/hours continuous maintenance	Aali et al. ^{7,****}	50	1.20 (0.30)	2.25 (0.75)	—	—	2.10 (0.85)	—	—	—	
	Handwerker et al. ^{22,****}	8	0.76 (0.05)	1.73 (0.14)	1.78 (0.13)	1.83 (0.13)	—	—	—	—	
	Sibai et al. ^{5,****}	7	—	—	1.86	1.87	1.94	2.00	2.10	1.84	
	Taber et al. ^{32,****}	9	0.90 (0.03)	—	—	—	2.38 (0.08)	—	—	1.99 (0.10)	
	Tongsong et al. ^{33,****}	25	—	—	—	2.27 (0.19)	2.33 (0.25)	—	—	—	
	Phuapradit et al. ^{26,****}	44	0.95 (0.12)	1.97 (0.16)	1.93 (0.16)	1.85 (0.12)	1.97 (0.12)	2.22 (0.12)	2.42 (0.12)	—	
	Apostol et al. ^{13,****}	16	—	—	—	—	—	—	—	2.05**	
6-g loading + 2 g/hour continuous maintenance	Chissell et al. ^{16,****}	8	0.80 (0.12)	1.90	1.75	1.70	1.75	1.80	1.80	—	
	Guzin et al. ^{21,****}	50	0.58 (0.21)	—	—	1.32 (0.26)	—	—	—	—	
	Mason et al. ^{25,****}	37	0.62 (0.01)	—	—	—	—	—	—	—	
	Singh et al. ^{30,****}	35	0.61 (0.17)	—	—	—	1.20	1.77	2.15	2.72	
	Thurnau et al. ^{34,****}	10	—	—	—	—	—	—	—	2.27**	
	Abbade et al. ^{12,****}	14	0.74 (0.12)	1.23 (0.16)	1.11 (0.12)	1.03 (0.16)	1.07 (0.12)	—	—	—	
	Dayicoglu et al. ^{19,****}	194	—	—	—	2.01 (0.33)	—	—	2.52 (0.43)	2.43 (0.34)	
2-g loading + 1.5 g/hour maintenance	Chesley and Tepper ^{3,****}	8	0.90	—	1.27	1.44	1.56	—	—	—	
	Chesley and Tepper ^{3,****}	3	0.74	—	0.95	0.90	—	—	—	—	
	Wright et al. ^{35,****}	25	0.81 (0.10)	1.99 (0.18)***	—	—	—	—	—	—	
	Lu et al. ^{23*,****}	51	1.08 (0.21)	—	—	—	—	—	—	—	
	Chen et al. ^{14,****}	30	0.92	—	2.16	—	—	—	—	2.16	
	7.5–10 g/hour loading + 7.5–10 g over 4 hours										

SD, standard deviation.

*Model-based study.

**Average concentration

***16 minutes after initiating infusion.

****Data only for women with pre-eclampsia.

*****Data not disaggregated for women with pre-eclampsia and eclampsia.

were all <1.00 mmol/l with mean values ranging between 0.74 and 0.85 mmol/l (Table 2). Following the loading dose, serum magnesium levels rose sharply to about twice the baseline levels at ½ hour (1.48–1.70 mmol/l). At 1, 2, and 4 hours of the maintenance dose, the mean serum levels remained at a fairly constant level that was consistent with the values attained at ½ hour. The serum levels at 8, 12, and 24 hours also remained within the same range and at no point did the mean serum concentration level reached 2.00 mmol/l. The described serum magnesium levels between ½ hour and 24 hours following initiation of treatment was consistent with the steady-state level of 1.64 mmol/l and an ‘average concentration’ of 1.70 mmol/l reported by two studies.^{5,17} One study showed that the peak serum concentration was achieved within half an hour of treatment.²⁴ The apparent volume of distribution estimated by two model-based studies varied considerably between the populations studied—15.60 l in a population of Indian women compared with 32.20 l in Australian women.^{17,27} However, the estimated plasma clearance was fairly consistent across the two populations—4.81 and 4.28 l/hour, respectively. One study estimated the half-life of MgSO₄ to be 5.2 hours.¹⁷ No other pharmacokinetic parameters were reported in the included studies.

4-g loading dose and 2 g/hour continuous maintenance infusion

Five studies reported pharmacokinetic data based on the use of this regimen.^{5,8,22,32,33} Following administration of the loading dose, serum magnesium concentration rose rapidly to double the baseline values by ½ hour (1.73–2.25 mmol/l). Data on mean serum concentrations at 1, 2, 4, 8, and 12 hours from the start of infusion showed a gradual rise in serum magnesium to a plateau level, with mean levels slightly above 2.00 mmol/l being more consistent after 4 hours. The fluctuations in the serum magnesium levels were minimal and the described pattern was consistent with the steady state concentrations of 1.84 and 1.99 mmol/l, as reported by two studies.^{5,32}

Based on this regimen, one study estimated the volume of distribution of magnesium to be 16.40 l, plasma clearance to be 1.21 l/hour and elimination half-life to be 20.2 hours.³² Three studies reported considerable variations in the ionised (free) magnesium fraction at baseline and during maintenance infusion.^{8,22,32} At baseline, the ionised fraction was between 50.0 and 64.9% of the total serum magnesium but these fractions appeared to decrease as the serum level approached steady-state levels. Two of these studies demonstrated no correlation between ionised and total magnesium,^{8,32} whereas the third study reported a strong correlation between ionised and total magnesium.²² This finding was supported by a report of a positive correlation of ionised and total magnesium in pre-eclamptic

women in another study.³⁶ No other pharmacokinetic parameters were reported in the included studies.

5-g loading dose and 1 g/hour continuous maintenance infusion

Based on this regimen, one study reported that serum magnesium rose rapidly from baseline level of 0.95 mmol/l to 1.97 mmol/l by ½ hour, followed by a gradual decline by 1 hour before rising slowly again to steady between 2.20 and 2.42 mmol/l between 12 and 24 hours of maintenance infusion.²⁶

6-g loading dose and 2 g/hour continuous maintenance infusion (Sibai regimen)

Six studies provided sparse pharmacokinetic data based on this regimen.^{13,16,21,25,30,34} The reported baseline serum magnesium values were between 0.58 and 0.80 mmol/l.^{16,21,25,30} Following initiation of MgSO₄, one study showed that this level doubled in ½ hour before declining slightly to plateau between 1.70 and 1.80 mmol/l between 1 hour and 12 hours of maintenance infusion.¹⁶ At no point during the treatment did the serum level reach 2.00 mmol/l (peak concentration of 1.96 mmol/l was attained at 0.90 hour). Another study recorded a similar pattern of rapid rise and fall in serum magnesium following the loading dose but the mean levels gradually increased to achieve levels above 2.00 mmol/l between 12 and 24 hours.³⁰ Two other studies also reported ‘average’ values of 2.05 and 2.27 mmol/l during administration of this regimen.^{13,34}

Two studies reported cerebrospinal fluid (CSF) magnesium levels of 1.23–1.34 mmol/l.^{13,34} One study reported no significant alteration in the baseline ionised fraction of 53.6% in the CSF despite considerable increase in serum magnesium during administration of MgSO₄ for periods of up to 48 hours.¹³ Baseline ionised magnesium in the serum was reported to be 69.8% in another study.²⁵

Other intravenous regimens

Table 2 also shows the available data for seven less popular intravenous regimens. With 4-g loading dose followed by 2 g/hour intermittent IV bolus injections, one study showed a rapid rise of serum magnesium from baseline value to a peak concentration of 1.64 mmol/l by 15 minutes, after which it fell very rapidly to 1.23 mmol/l by 2 hours.¹² The first maintenance bolus dose at 2 hours was accompanied by another peak (1.69 mmol/l) and rapid fall to 1.07 mmol/l at 4 hours. For the most of the 4-hour follow up of post-dose serum concentration, the mean levels of magnesium remained around 1.00 mmol/l.

A study that administered a 4.5-g loading dose and 1.8 g/hour maintenance dose reported a gradual serum magnesium rise from 2.01 mmol/l at 2 hours to a peak of

2.52 mmol/l at 12 hours before it declined to 2.43 mmol/l at 24 hours.¹⁹ Another study evaluating the pharmacokinetics of lower intravenous regimen (2 g loading plus 1.5 g/hour continuous infusion) to women with eclampsia showed a very slow rise in mean serum magnesium levels from 1.27 at 1 hour to 1.56 mmol/l at 4 hours.³ Data (not shown) showed that the level remained sustained at <2 mmol/l by 6 hours of maintenance. The same study reported serum concentration-time data for a 2-g loading dose only for three eclamptic women.³ The study showed a transitory and trivial effect on the baseline magnesium—peaking within 10 minutes of injection and falling rapidly to 0.90 mmol by 2 hours.

One study estimated the initial volume of distribution based on a single intravenous injection of 4 g of MgSO₄ to women with pre-eclampsia to be 13.65 l.²⁵ Another study used an experimental weight-based regimen (120 mg/kg loading dose and 24 mg/kg maintenance dose over 5 hours) and estimated the volume of distribution to be 49 l (central and peripheral) and total clearance to be 5 l/hour.²³ Simulations based on the model developed by the same study showed that maintenance infusion rate of 1 g/hour produced concentrations well below 2.00 mmol/l and rarely produced concentrations >2.00 mmol/l during the first 10 hours of drug administration, whereas 2 g/hour infusion rate had higher probability of achieving concentrations within 2.00 and 4.00 mmol/l and lower probability of excess values.

Based on a regimen that included a 7.5–10 g loading dose, fast infusion over 1 hour and maintenance infusion of 7.5–10 g over 4 hours in 30 women with pre-eclampsia, one study showed a rapid rise in magnesium level to over twice the baseline levels, reaching a steady state of 2.16 mmol/l.¹⁴

Intramuscular MgSO₄ regimens

4-g IV and 10-g IM loading dose, and 5-g IM maintenance dose every 4 hours (Pritchard regimen)

Six studies provided serum magnesium concentration-time data based on this regimen.^{5,14,18,27–29} Reported baseline magnesium levels were <1.00 mmol/l (Table 3). Following the loading dose, serum magnesium level rose sharply from the baseline to at least two-fold by ½ hour (1.90–2.79 mmol/l). After the initial rise, Chissell et al. reported a slight decline in serum magnesium at 1 hour but relatively steady levels between 1.60 and 1.75 mmol/l until 12 hours of the maintenance injection.¹⁶ In the same study, serum level peaked at 2.07 mmol/l at 1½ hours following the initiation of treatment.

Sibai et al.⁵ showed a rapid rise in the first 4 hours with values all above 2.00 mmol/l and a slight decline by 8 and 12 hours. Singh et al. reported a similar pattern with a

gradual increase demonstrated between 4 and 24 hours following initiation of treatment.³⁰ Ekele and Badung also showed a more than two-fold rise in serum magnesium compared with baseline and mean levels slightly above 2.00 mmol/l at 8 and 12 hours of maintenance injections.²⁰ Shreya et al.²⁹ also reported a similar increase in serum magnesium level in the first ½ hour and values slightly lower than 2.00 mmol/l at 4 hours. Overall, the serum-concentration data fluctuated much more with this regimen than with continuous intravenous regimens described above, and serum level versus time data were less consistent across studies. However, for every time point reported, there were mean values reaching ≥2.00 mmol/l, but none reached 3.00 mmol/l.

Only one study reported on magnesium sulphate toxicity using this regimen. The study reported respiratory depression and death in a woman with a serum magnesium level of 9.90 mmol/l.³¹

10-g IM loading dose and 5-g IM maintenance dose every 4 hours

Two studies reported serum-concentration data based on this regimen.^{3,5} In one of the studies, the mean levels of serum magnesium at 1, 2, and 4 hours were observed to be 1.36, 1.56, and 1.48 mmol/l, respectively.³ The other study only reported a steady state level of 1.83 mmol/l.⁵

3-g IV and 10-g IM (13 g) loading dose only

With this regimen, one study reported a baseline serum magnesium of 2.10 mmol/l.¹⁵ The mean magnesium levels rose to 2.25 and 2.30 mmol/l at 1 and 2 hours following treatment, respectively, and gradually declined at 4 hours to 1.90 mmol/l.

Other intramuscular regimens

One study reported serum magnesium levels following the administration of a single 10-g IM loading dose.³ Mean serum magnesium concentration rose slowly to attain its average peak of 1.81 mmol/l between 1½ and 2 hours before it declined to 1.44 and 1.34 mmol/l at 4 and 6 hours, respectively. Another study reported a steady-state level of 1.50 mmol/l following a single 12-g loading dose regimen.²⁸ Using a single dose of 4 g MgSO₄ intravenously and 4 g intramuscularly, another study reported that the mean serum level increased notably in the first ½ hour and then gradually decreased to levels similar to those achieved by the 10-g IM loading dose-only regimen.²⁹

Discussion

Main findings

This review shows that the bioavailability for all intravenous regimens is complete and rapid as expected, and

Table 3. Serum magnesium concentration-time profile for intramuscular regimens

Regimen	Study	n	Mean serum magnesium in mmol/l (SD)								Steady state
			Baseline	½ hour	1 hour	2 hours	4 hours	8 hours	12 hours	24 hours	
4-g (IV) + 10-g IM loading + 5-g 4 hourly maintenance	Chissell et al. ^{16*}	9	0.74	1.90	1.80	1.75	1.75	1.75	1.60	—	—
	Sibai et al. ^{5*}	8	—	2.79	2.79	2.63	2.10	1.97	1.93	—	2.71
	Singh et al. ^{30***}	35	0.64	—	—	—	1.36	1.85	2.14	2.59	—
	Ekele and Badung ^{20**}	19	0.72 (0.10)	—	—	—	1.90 (0.23)	2.21 (0.11)	2.18 (0.10)	—	—
	Shreya et al. ^{29**}	18	0.81 (0.10)	2.45 (0.43)	—	—	1.88 (0.51)	—	—	—	—
3-g (IV) loading + 10-g (IM) maintenance	Shreya et al. ^{29*}	22	0.78 (0.11)	2.60 (0.53)	—	—	1.97 (0.47)	—	—	—	—
	Chesley and Tepper ^{3*}	3	—	—	2.30	2.30	1.90	—	—	—	—
	Chesley ^{15*}	10	2.10	—	2.25	2.25	1.90	—	—	—	—
	Chesley and Tepper ^{3*}	Unspecified	—	—	1.36	1.56	1.48	—	—	—	—
10-g loading + 5 g (4 hourly) maintenance	Sibai et al. ^{5*}	10	—	—	—	—	—	—	—	—	1.83
	Chesley and Tepper ^{3*}	20	0.82	—	1.52	1.81	1.44	—	—	—	—
	Seydoux et al. ^{28*}	5	0.80	—	—	—	—	—	—	—	1.50
4-g IV, 4-g IM loading dose only	Shreya et al. ^{29**}	9	0.73 (0.09)	1.94 (0.51)	—	—	1.49 (0.23)	—	—	—	—
	Shreya et al. ^{29*}	31	0.78 (0.15)	1.83 (0.35)	—	—	1.46 (0.27)	—	—	—	—

SD, standard deviation.

*Data for women only with pre-eclampsia.

**Data for women only with eclampsia.

***Data not disaggregated for women with pre-eclampsia and eclampsia.

suggests a substantial bioavailability for the intramuscular regimens. Baseline serum magnesium concentrations were consistently <1 mmol/l. An intravenous loading dose of 4–6 g was associated with a rapid doubling of this baseline concentration within $\frac{1}{2}$ hour of starting the injection. A maintenance infusion of 1 g/hour following a 4-g loading dose (Zuspan regimen) consistently produced mean concentrations between 1 and 2 mmol/l throughout the period of administration. Maintenance infusion of 2 g/hour following either a 4- or a 6-g loading dose had a higher likelihood of producing mean concentrations between 2 and 3 mmol/l with fewer fluctuations during the period of administration. Intermittent bolus injections of 2 g produced a spike in serum concentrations that fell very rapidly to almost basal levels within 2 hours of injection. The Pritchard regimen inconsistently produced serum concentrations between 2 and 3 mmol/l but the repeated intramuscular injections resulted in more fluctuations compared with continuous intravenous maintenance regimens. The volume of distribution of magnesium varied significantly but plasma clearance was fairly similar across populations.

Strengths and limitations

To our knowledge, this is the first systematic review of clinical pharmacokinetic properties of MgSO_4 when used for prevention and treatment of eclampsia. We minimised potential bias in the review process by searching major databases without language or date restrictions to capture all relevant studies as far back as the 1950s.

The main limitation of this review was the inclusion of pharmacokinetic parameters from different study designs with varying primary objectives and study characteristics. However, we minimised potential bias by avoiding meta-analysis and performing descriptive syntheses of available pharmacokinetic data, thus taking advantage of the available knowledge on the subject without compromising methodological rigour of a systematic review. Another limitation is the inclusion of studies that combined data of women with pre-eclampsia and eclampsia, which precluded a clear description of pharmacokinetics according to disease severity. Nevertheless, the proportion of women with eclampsia in the included studies is unlikely to impact significantly on the patterns described.

Interpretations

Although there is no consensus on the magnesium concentration required to prevent or treat eclamptic seizures, serum concentrations between 2 and 3.5 mmol/l (4–7 mEq/l) are generally held to be therapeutic and have directly and indirectly driven clinical practice for decades.⁶ However, there is no evidence from our review that concentrations within this range are consistently achieved even by the two most popular and clinically efficacious regimens

(Zuspan and Pritchard).^{1,2} This suggests that the minimum effective serum magnesium concentration is likely to be lower and the therapeutic window wider than generally accepted levels.

Of particular interest is the maintenance dose of the Zuspan regimen, which was associated with a steady-state level that was well below 2 mmol/l. Similar observations have led some researchers to advocate higher intravenous loading and maintenance doses to match serum levels achieved by the Pritchard regimen in order to increase therapeutic efficacy.²⁷ It is important to note, however, that a substantial proportion of women receiving the Pritchard regimen are also below the 'therapeutic range' at varying time points during the course of treatment. Interestingly, the clinical efficacy in terms of seizure prophylaxis for both regimens is generally considered comparable.^{1,2} As higher doses risk excessive serum magnesium levels and toxicity, the noted differences in the associated serum concentrations do not justify a review of the Zuspan dosing regimen.

Our findings highlight the disconnection between the pharmacokinetics and choice of alternative MgSO_4 regimens for treating women with pre-eclampsia and eclampsia. For instance, the use of a 2-g loading dose only or a 2 g/hour bolus IV injection only produces transient and trivial effects on the serum magnesium concentrations and is unlikely to be clinically effective. On the other hand, the review provides support for the clinical non-inferiority shown by some regimens. For example, the fact that the 10-g IM loading dose-only regimen produced serum levels similar to the Zuspan regimen for up to 6 hours may explain the reported comparative efficacy of Pritchard regimens in settings where prompt delivery of women with pre-eclampsia and eclampsia is possible.

Conclusions

It would be useful to consider what is known about the basic pharmacokinetic profile of MgSO_4 when selecting dosage regimens of unproven efficacy for clinical use. As evident from the serum levels attained during treatment with the Zuspan regimen, it appears that MgSO_4 can be protective even with serum concentrations of <2 mmol/l. Therefore, titrating MgSO_4 injections to achieve a pre-set therapeutic range of 2–3.5 mmol may risk toxic levels without necessarily improving clinical protection against seizures. Regardless of the slight differences in the pharmacokinetic profiles of the two currently recommended regimens, the comparability of their clinical efficacy is reassuring and does not justify a further increase in the total dose of MgSO_4 for prophylaxis and treatment of eclampsia. The single or intermittent use of intravenous bolus injection of 2 g MgSO_4 does not produce a sus-

tained increase in serum magnesium levels to provide a clinically meaningful protection against seizures and is best avoided.

Most of the studies included in this review had small numbers of participants and the majority did not report on the full pharmacokinetic properties of MgSO_4 . In future research, efforts should be made to investigate the complete profile for any particular regimen with separate data for pre-eclampsia and eclampsia. The demonstrated serum magnesium levels achieved by clinically efficacious regimens can be targeted in standard pharmacokinetic-pharmacodynamic (PK/PD) modelling and simulation studies to determine the minimum effective dosage of MgSO_4 for prophylaxis and treatment of eclampsia.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

OTO and AMG conceived the study. OTO prepared the study protocol with input from AMG and BOO. BOO and OTO performed initial screening of search outputs, identified eligible studies and extracted data. QL updated the search and along with BOO, screened the updated search outputs for eligible studies. BOO and OTO drafted the manuscript. BOO, OTO, QL, PL, GC, ZQ, LD, JPS, and AMG interpreted the data and revised the manuscripts for intellectual contents. All authors approved the manuscript for publication.

Details of ethics approval

No ethical approval was required for this study.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Risk of bias assessment of the included studies.

Figure S2. Risk of bias assessment for intravenous regimens.

Figure S3. Risk of bias assessment for intramuscular regimens.

Table S1. Checklist for risk of bias assessment and explanations.

Table S2. Characteristics of included studies.

Table S3. Characteristics of excluded studies and reasons for exclusion.

Table S4. Risk of bias assessment of included studies.

Box S1. References to excluded studies. ■

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RESEARCH ARTICLE

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Searching for the definition of macrosomia through an outcome-based approach in low- and middle-income countries: a secondary analysis of the WHO Global Survey in Africa, Asia and Latin America

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Abstract

Background: No consensus definition of macrosomia currently exists among researchers and obstetricians. We aimed to identify a definition of macrosomia that is more predictive of maternal and perinatal mortality and morbidity in low- and middle-income countries.

Methods: We conducted a secondary data analysis using WHO Global Survey on Maternal and Perinatal Health data on Africa and Latin America from 2004 to 2005 and Asia from 2007 to 2008. We compared adverse outcomes, which were assessed by the composite maternal mortality and morbidity index (MMMI) and perinatal mortality and morbidity index (PMMI) in subgroups with birthweight (3000–3499 g [reference group], 3500–3999 g, 4000–4099 g, 4100–4199 g, 4200–4299 g, 4300–4399 g, 4400–4499 g, 4500–4999 g) or country-specific birthweight percentile for gestational age (50th–74th percentile [reference group], 75th–89th, 90th–94th, 95th–96th, and ≥97th percentile). Two-level logistic regression models were used to estimate odds ratios of MMMI and PMMI.

Results: A total of 246,659 singleton term births from 363 facilities in 23 low- and middle-income countries were included. Adjusted odds ratios (aORs) for intrapartum caesarean sections exceeded 2.0 when birthweight was greater than 4000 g (2.00 [95 % CI: 1.68, 2.39], 2.42 [95 % CI: 2.02, 2.89], 2.01 [95 % CI: 1.74, 2.33] in Africa, Asia and Latin America, respectively). aORs of MMMI reached 2.0 when birthweight was greater than 4000 g, 4500 g in Asia and Africa, respectively. aORs of PMMI approached to 2.0 (1.78 [95 % CI: 1.16, 2.74]) when birthweight was greater than 4500 g in Latin America. When birthweight was at the 90th percentile or higher, aORs of MMMI and PMMI increased, but none exceeded 2.0.

Conclusions: The population-specific definition of macrosomia using birthweight cut-off points irrespective of gestational age (4500 g in Africa and Latin America, 4000 g in Asia) is more predictive of maternal and perinatal adverse outcomes, and simpler to apply compared to the definition based on birthweight percentile for a given gestational age.

Keywords: Macrosomia, Maternal mortality, Maternal morbidity, Neonatal mortality, Neonatal morbidity

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Background

“Macrosomia” is a term that describes a very large fetus or neonate. The condition may be caused by constitutional/genetic factors, maternal obesity and/or excessive gestational weight gain, or maternal hyperglycemia due to pre-existing diabetes or gestational diabetes that were not adequately controlled [1]. In low-and middle- income countries (LMICs) or settings where antenatal care is sub-optimal, poorly controlled diabetes or undiagnosed gestational diabetes may be a more important cause for macrosomia than in high-income countries, where antenatal care is better. In high-income countries, the prevalence of macrosomia has been increasing in the last two to three decades [2, 3]. But in many LMICs, macrosomia is still not perceived to have the same priority as other public health problems (e.g., HIV) [4]. However, with the increasing prevalence of maternal obesity and diabetes [5, 6] a parallel increase in macrosomic infants might be expected in LMICs. Complicated deliveries related to macrosomia could lead to more severe adverse outcomes in resource-poor settings due to limited availability of obstetric care. Thus, a precise definition of macrosomia that is more predictive of maternal and perinatal mortality and morbidity is needed. In this study, we aimed to explore a definition through an outcome-based approach and comparing commonly used definitions currently.

Currently, no consensus definition exists among researchers and obstetricians. The most commonly used definition is based on birthweight cut-off points (e.g., 4000 g or 4500 g) [3, 7–9]. As it is increasingly recognized that racial variation in birthweight is substantial, more and more studies are using specific birthweight percentiles as cut-off points at a given gestational week (e.g., P_{90} or P_{97}) based on the concept of large-for-gestational-age (LGA) [2, 10]. Furthermore, most studies on macrosomia have focused on Caucasian populations in high-income countries, and very few studies on the topic focus on LMICs [2].

In this study we analyzed data from 23 LMICs in Africa, Asia, and Latin America that participated in the World Health Organization (WHO) Global Survey on Maternal and Perinatal Health (2004–2008). We assessed commonly used definitions of the term ‘macrosomia’ through an outcome-based approach. Two types of definitions were compared: one based on empirical absolute birthweight and the other on the country-specific birthweight percentile at each gestational week. We aimed to identify a definition that was more predictive of maternal and perinatal mortality and morbidity in term pregnancies in LMICs, which also takes into account regional variation.

Methods

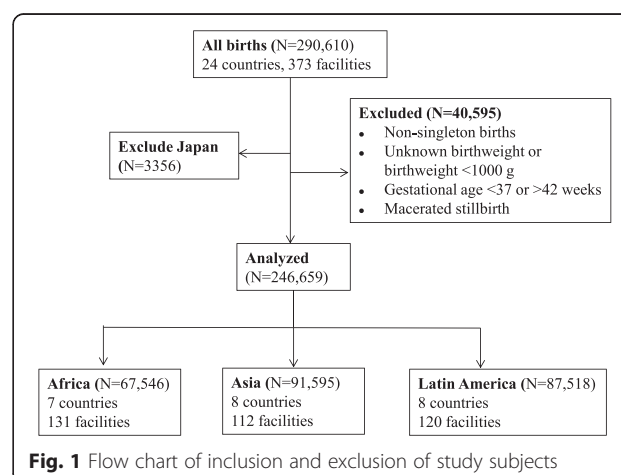
Study design and data extraction

The general objective of the WHO Global Survey on Maternal and Perinatal Health was to create a global

database on health services and outcomes for maternal and perinatal health, which concentrated on the relationship between mode of delivery and perinatal outcomes [2, 11]. This survey has previously been described in detail elsewhere [2, 11, 12]. A total of 373 facilities in 24 countries in Africa, Asia and Latin America participated in this survey. Data collection was carried out in 2004–05 in Africa and Latin America, and in 2007–08 in Asia. Trained data collectors extracted data from medical records and completed standardized forms. Gestational age was calculated based on the difference between the estimated and actual delivery date in the medical records. Data related to outcomes were obtained until discharge from the hospital. Maternal weight was defined differently as described previously: in Africa and Latin America, maternal weight was the weight recorded at the first antenatal care visit, while in Asia it was the weight at the last visit before delivery [2, 11].

This is a secondary data analysis using data from the WHO Global Survey on Maternal and Perinatal Health. The protocol of this survey was approved by the ethics committees at the WHO and in all participating centres [11]. We obtained permission to use this data from Department of Reproductive Health and Research, WHO. An individual informed consent was not obtained because in this survey data were extracted from medical records without individual identification [11].

For the purpose of this analysis, the study sample was restricted to: 1) LMICs; 2) singleton pregnancies; 3) live births or fresh stillbirth; 4) birthweight ≥ 1000 g; and 5) term births (gestational age 37–42 weeks). As the analysis focused on LMICs, Japan was excluded. Macerated stillbirths were also excluded, as we were interested in mortality associated with delivery, but not pre-delivery mortality. Infants who had missing information on birthweight or gestational age were also excluded. The sample selection process is shown in Fig. 1.



Statistical analysis

Previous studies have shown that the perinatal mortality rate decreases with increasing birthweight or birthweight percentile until it reaches an inflection point, after which a further rise in birthweight increases the mortality, i.e., a reversed J-shaped mortality curve [13–17]. We applied this principle to our analysis: macrosomia was defined as a birthweight or birthweight percentile that exceeds the nadir of the mortality curve, and at which point the relative risk of perinatal mortality is twice or greater than that of the nadir. We used *a priori* odds ratio of 2.0 as a criterion for clinical significance, as per previous studies [18, 19].

We used the birthweight range of 3000–3499 g or at 50th–74th percentiles as the reference groups because our exploratory analyses showed that the nadir of the birthweight-specific mortality rate fell into these ranges. According to the exploratory analyses, there was no significant difference of risks of neonatal mortality and morbidity among subgroups of every 100 g between 3500 and 4000 g. Thus, infants with birthweights in the range of 3500–3999 g were combined as one subgroup. Birthweights between 4000 and 4500 g were categorized into subgroups of every 100 g in order to explore the cut-off point for the definition of macrosomia.

To calculate weight percentiles, we adopted the global reference for fetal and birth weight percentile [20]. Briefly, based on the mean birthweight and variation at 40 weeks of gestation at each country, country-specific, equation-derived (i.e., not empirical) birthweight reference percentiles at 75th, 90th, 95th and 97th for each gestational week were generated. Infant birthweight was categorized according to these references.

The adverse maternal outcomes included maternal mortality and severe morbidity defined as any of the following: admission to an intensive-care unit (ICU), referral to a higher level or special care unit, blood transfusion, hysterectomy, vesico-vaginal/recto-vaginal fistula and third or fourth degree perineal laceration. The adverse perinatal outcomes were still-birth, early neonatal death (neonatal death within 7 days of birth) and severe neonatal morbidity defined as any of the following: admission to a Neonatal ICU for 7 days or more, referral to a higher level or special care unit and 5-min Apgar score less than four. As maternal and perinatal mortality and severe morbidity are rare outcomes, the composite maternal mortality and morbidity index (MMMI) and perinatal mortality and morbidity index (PMMI) were computed [2]. The MMMI and PMMI were coded as an event if mortality or any of the corresponding severe morbidity occurred. We also compared the risks of caesarean section and assisted vaginal delivery (forceps/vacuum extraction) for subgroups of infants by birthweight and birthweight percentile.

Two-level logistic regression models were used to estimate odds ratios (ORs) of maternal and perinatal mortality and morbidity by absolute birthweight and birthweight percentile for gestational age. Facilities represented units at level two and individuals within facilities were observations at level one. To take into account the large variations of anthropometry among regions, we stratified the analysis by region (Africa, Asia and Latin America). We adjusted for country, maternal age, marital status, education (total years of school attendance), obesity (maternal body mass index, BMI ≥ 30 kg/m²), pre-existing diabetes, parity, infant sex, and gestational age as potential confounders according to previous literature [7, 10]. All analyses were conducted with SAS version 9.2 (SAS Institute Inc, Cary, NC).

Maternal weight and/or height, and consequently maternal BMI, were missing in more than 10 % of the study population in Kenya (85 %), Brazil (67 %), Angola (43 %), Argentina (33 %), Uganda (21 %) and Peru (13 %). A missing category within “maternal obesity” (BMI ≥ 30 kg/m²) was therefore created and included in all regression models. In our sensitivity analysis, we restricted our calculations to countries with less than 10 % of the missing value for BMI. The “(pre-existing) diabetes mellitus” variable was missing in less than 1 % of the study population of each region. For the estimation of risks of MMMI and PMMI by birthweight or birthweight percentile, we performed a sensitivity analysis by excluding the variables “maternal obesity” and “diabetes” from the regression models. In another sensitivity analysis, we compared the adjusted odds ratios (aORs) of MMMI and PMMI in subgroups using birthweight percentile of the study population as cut-off points, the results were essentially unchanged (data not shown). In another sensitivity analysis, we compared the aORs of MMMI and PMMI in subgroups using the empirical country- and gestational-age-specific birthweight percentile of the study population as cut-off points, the results were essentially unchanged (not shown).

Results

A total of 246,659 deliveries at 363 facilities in 23 LMICs were included in this analysis (Fig. 1). Large variations in birthweight distribution were observed among infants in the three regions. Mean birthweight was 3037 g, 3225 g and 3253 g in Asia, Africa and Latin America, respectively, and the proportion of infants with a birthweight greater than 4500 g was 0.3 %, 1.2 %, and 0.7 % across these three regions. The prevalence of birthweight greater than the 97th percentile was 7.2 % (Latin America), 10.1 % (Africa) and 10.5 % (Asia) in the three regions (Table 1). In all three regions, the proportion of maternal age older than 35 years, maternal obesity (BMI ≥ 30 kg/m²), maternal preexisting gestational diabetes, multiparas and infant

Table 1 Country-specific birthweight distribution of singleton term births

	N	Birthweight (g)			Birthweight percentile		
		Mean (SD)	≥4000 (%)	≥4500 (%)	≥P ₉₀ (%)	≥P ₉₅ (%)	≥P ₉₇ (%)
Africa	67546	3225 (489)	7.3	1.2	20.6	12.8	10.1
Angola	3304	3125 (473)	3.1	0.7	20.8	12.8	10.4
Algeria	14361	3469 (501)	15.2	3.2	15.4	9.1	6.9
Democratic Republic of Congo	6989	3077 (452)	2.7	0.3	22.6	15.4	11.6
Kenya	16091	3158 (448)	3.9	0.5	23.6	15.8	12.6
Nigeria	7721	3059 (442)	2.0	0.1	16.4	10.7	8.1
Niger	7296	3215 (494)	8.0	1.5	19.2	10.5	8.4
Uganda	11784	3252 (464)	9.1	0.8	25.2	14.6	12.2
Asia	91595	3037 (464)	2.5	0.3	20.3	13.8	10.5
Cambodia	5052	3090 (419)	2.5	0.5	16.6	11.2	9.1
China	13595	3333 (419)	7.2	0.7	17.6	10.0	7.2
India	18828	2772 (424)	0.6	0.0	28.2	22.2	16.6
Nepal	7316	2958 (469)	1.7	0.2	18.0	12.2	8.4
Philippines	11946	2961 (425)	1.1	0.2	19.0	12.2	9.1
Sri Lanka	13787	2980 (424)	1.3	0.1	20.3	13.9	10.5
Thailand	8621	3137 (437)	2.5	0.3	20.9	13.5	10.1
Vietnam	12450	3209 (404)	3.5	0.3	14.8	8.7	8.0
Latin America	87518	3253 (455)	5.5	0.7	15.7	9.7	7.2
Argentina	9592	3345 (453)	7.5	1.1	12.8	7.4	5.0
Brazil	13373	3223 (446)	4.4	0.5	14.8	9.2	6.7
Cuba	11817	3316 (459)	7.6	1.0	15.6	9.7	7.1
Ecuador	11359	3117 (440)	2.9	0.3	14.7	9.8	6.7
Mexico	18653	3199 (444)	4.1	0.5	17.5	10.5	8.2
Nicaragua	5188	3157 (435)	3.0	0.3	21.6	14.9	11.7
Paraguay	3051	3389 (472)	10.2	1.8	16.3	10.1	7.4
Peru	14485	3348 (442)	7.4	0.9	14.8	9.0	6.6

male sex was positively associated with higher birthweight (all p values <0.0001 , Additional file 1: Table S1).

The overall rates of caesarean deliveries (and intrapartum rate) in Africa, Asia and Latin America were 12.0 % (6.2 %), 28.0 % (12.5 %) and 34.1 % (12.0 %) ($p < 0.0001$), respectively. Table 2 shows that compared with the reference group (3000–3499 g), aORs of elective and intrapartum caesarean section exceeded 2.0 when birthweight was greater than 4000 g in all three regions, while the risks of forceps or vacuum extraction did not rise significantly in most subgroups of infants in Asia and Latin America. In Africa, the aORs of forceps or vacuum extraction reached 2.0 when birthweight exceeded 4500 g. There was a large variation of elective caesarean section rate among populations. In Africa, only around 5 % suspected macrosomic babies were born through elective caesarean section while in Asia and Latin America, the responding rate was as high as around 40 and 20 %, respectively. The association between caesarean section and

birthweight seemed less pronounced when infants were categorized by birthweight percentile and aORs hardly reached 2.0 (Table 3). The most important indication for CS for suspected macrosomic cases in all populations were cephalopelvic disproportion, followed by previous caesarean and fetal distress. Around 40 % of suspected macrosomic cases born through caesarean had an indication of previous caesarean section. The other two indications accounted for around 30 and 20 % caesarean deliveries, respectively (Additional file 2: Table S2).

The birthweight-specific risks of MMMI and PMMI are presented in Fig. 2. The association is expressed in a reverse “J”- or “U”-shaped curves. In all three regions, the lowest risk of MMMI corresponded to the birthweight range of 3000–3500 g, which was used as the reference group. When the birthweight exceeded 3500 g, aORs of MMMI increased gradually. The aORs of MMMI reached 2.0 when birthweight was greater than 4000 g, 4500 g and 5000 g in Asia, Africa and Latin

Table 2 Prevalence and odds ratios of elective caesarean, intrapartum caesarean section and forceps or vacuum extraction by birthweight

Birthweight (g)	N	Elective caesarean section			Intrapartum caesarean section			Forceps extraction or vacuum extraction		
		Prevalence (%)	Adjusted OR (95 % CI) ^a	<i>p</i> value	Prevalence (%)	Adjusted OR (95 % CI) ^a	<i>p</i> value	Prevalence (%)	Adjusted OR (95 % CI) ^a	<i>p</i> value
Africa	67546									
3000–3499	28788	1.9	1.00	–	5.8	1.00	–	1.8	1.00	–
3500–3999	15824	2.3	1.19 (1.03, 1.39)	0.0196	6.4	1.27 (1.16, 1.38)	<0.0001	2.4	1.22 (1.05, 1.41)	0.0094
4000–4099	2154	2.1	1.14 (0.79, 1.63)	0.4824	9.0	2.00 (1.68, 2.39)	<0.0001	2.9	1.81 (1.35, 2.44)	0.0001
4100–4199	670	4.2	1.96 (1.25, 3.07)	0.0032	8.1	1.87 (1.38, 2.53)	0.0001	3.4	1.64 (1.03, 2.6)	0.0358
4200–4299	686	5.0	2.61 (1.72, 3.96)	<0.0001	9.6	2.36 (1.78, 3.12)	<0.0001	2.2	1.09 (0.63, 1.88)	0.7618
4300–4399	377	2.0	0.83 (0.36, 1.93)	0.6687	10.6	2.39 (1.67, 3.42)	<0.0001	2.7	0.98 (0.50, 1.92)	0.9555
4400–4499	239	5.7	3.26 (1.67, 6.34)	0.0005	8.8	2.48 (1.52, 4.04)	0.0003	3.3	1.84 (0.86, 3.93)	0.1131
4500–4999	648	6.3	3.62 (2.40, 5.46)	<0.0001	13.0	3.78 (2.90, 4.92)	<0.0001	3.7	2.17 (1.37, 3.42)	0.0009
≥ 5000	146	5.0	2.99 (1.12, 7.95)	0.0287	14.4	5.11 (3.00, 8.72)	<0.0001	8.9	8.34 (4.22, 16.5)	<0.0001
Asia	91595									
3000–3499	36479	11.8	1.00	–	13.2	1.00	–	2.7	1.00	–
3500–3999	13539	18.3	1.36 (1.27, 1.47)	<0.0001	18.6	1.44 (1.36, 1.53)	<0.0001	2.6	1.27 (1.12, 1.45)	0.0003
4000–4099	945	31.6	2.33 (1.90, 2.86)	<0.0001	24.1	2.42 (2.02, 2.89)	<0.0001	2.1	1.64 (1.02, 2.64)	0.0413
4100–4199	492	34.8	2.32 (1.76, 3.07)	<0.0001	26.6	2.61 (2.05, 3.33)	<0.0001	2.2	1.69 (0.87, 3.29)	0.1195
4200–4299	320	40.3	3.19 (2.28, 4.47)	<0.0001	28.1	3.79 (2.77, 5.18)	<0.0001	3.1	2.73 (1.37, 5.46)	0.0045
4300–4399	183	40.5	2.63 (1.70, 4.07)	<0.0001	30.1	3.29 (2.22, 4.88)	<0.0001	2.2	2.56 (0.87, 7.55)	0.0884
4400–4499	101	47.6	3.45 (1.90, 6.25)	<0.0001	29.7	4.13 (2.38, 7.15)	<0.0001	2.0	1.92 (0.42, 8.67)	0.3969
4500–4999	200	50.0	5.48 (3.45, 8.70)	<0.0001	30.0	5.20 (3.45, 7.83)	<0.0001	2.0	2.47 (0.81, 7.57)	0.1124
≥ 5000	52	40.0	4.20 (1.71, 10.34)	0.0018	32.7	9.44 (3.99, 22.35)	<0.0001	1.9	2.38 (0.3, 18.81)	0.4113
Latin America	87518									
3000–3499	38930	15.3	1.00	–	11.2	1.00	–	1.2	1.00	–
3500–3999	20875	16.9	1.19 (1.13, 1.26)	<0.0001	14.0	1.28 (1.21, 1.35)	<0.0001	1.5	1.51 (1.30, 1.77)	<0.0001
4000–4099	1675	21.7	1.64 (1.40, 1.91)	<0.0001	18.1	2.01 (1.74, 2.33)	<0.0001	0.7	0.80 (0.43, 1.48)	0.4699
4100–4199	1020	23.0	1.92 (1.58, 2.34)	<0.0001	19.1	2.19 (1.83, 2.62)	<0.0001	1.3	1.45 (0.79, 2.65)	0.2318
4200–4299	757	25.1	2.01 (1.60, 2.51)	<0.0001	21.7	2.48 (2.03, 3.03)	<0.0001	1.5	1.88 (0.99, 3.58)	0.0551
4300–4399	466	22.6	1.95 (1.45, 2.61)	<0.0001	24.4	3.00 (2.35, 3.84)	<0.0001	0.9	0.90 (0.32, 2.50)	0.8354
4400–4499	281	28.7	2.59 (1.83, 3.66)	<0.0001	19.6	2.66 (1.89, 3.73)	<0.0001	1.1	1.81 (0.55, 5.94)	0.3257
4500–4999	569	38.1	3.66 (2.87, 4.68)	<0.0001	23.8	4.17 (3.29, 5.3)	<0.0001	1.1	1.98 (0.84, 4.63)	0.1163
≥ 5000	55	35.3	3.54 (1.67, 7.53)	0.0010	20.0	3.13 (1.43, 6.85)	0.0045	3.6	4.64 (0.95, 22.64)	0.0579

^aAll estimates were based on two-level logistic regression models. Facilities represent units at level two and individuals within facilities are observations at level one. We adjusted for country, maternal age, marital status, education (total years of school attendance), obesity, diabetes, parity, infant sex, and gestational age

Table 3 Prevalence and odds ratios of elective caesarean, intrapartum caesarean section and forceps or vacuum extraction by birthweight percentile

Birthweight percentile	N	Elective caesarean section			Intrapartum caesarean section			Forceps extraction or vacuum extraction		
		Prevalence (%)	Adjusted OR (95 % CI) ^a	<i>p</i> value	Prevalence (%)	Adjusted OR (95 % CI) ^a	<i>p</i> value	Prevalence (%)	Adjusted OR (95 % CI) ^a	<i>p</i> value
Africa	67546									
P ₅₀ –P ₇₄	15747	1.8	1.00	–	5.5	1.00	–	1.9	1.00	–
P ₇₅ –P ₈₉	10150	2.3	1.31 (1.08, 1.59)	0.0067	6.5	1.23 (1.10, 1.38)	0.0002	1.8	1.18 (0.97, 1.44)	0.1032
P ₉₀ –P ₉₄	5247	2.5	1.36 (1.08, 1.72)	0.0093	6.0	1.25 (1.09, 1.44)	0.0019	1.8	1.39 (1.08, 1.78)	0.0106
P ₉₅ –P ₉₆	1820	3.6	1.91 (1.40, 2.60)	<0.0001	6.8	1.46 (1.18, 1.79)	0.0004	1.2	1.02 (0.64, 1.62)	0.9335
≥ P ₉₇	6851	3.8	2.00 (1.64, 2.44)	<0.0001	9.0	2.17 (1.92, 2.44)	<0.0001	1.7	1.86 (1.46, 2.37)	<0.0001
Asia	91595									
P ₅₀ –P ₇₄	18066	12.3	1.00	–	12.5	1.00	–	2.6	1.00	–
P ₇₅ –P ₈₉	14694	12.1	1.08 (1.00, 1.18)	0.0611	12.8	1.11 (1.03, 1.19)	0.0056	2.5	1.08 (0.93, 1.25)	0.3198
P ₉₀ –P ₉₄	5955	16.1	1.22 (1.10, 1.36)	0.0002	14.9	1.37 (1.25, 1.51)	<0.0001	2.2	1.05 (0.86, 1.29)	0.6286
P ₉₅ –P ₉₆	3030	14.5	1.31 (1.14, 1.51)	0.0002	13.4	1.60 (1.41, 1.82)	<0.0001	3.2	1.67 (1.32, 2.11)	<0.0001
≥ P ₉₇	9574	18.1	1.65 (1.50, 1.81)	<0.0001	17.2	1.90 (1.75, 2.06)	<0.0001	3.0	1.55 (1.31, 1.83)	<0.0001
Latin America	87518									
P ₅₀ –P ₇₄	20003	15.8	1.00	–	12.3	1.00	–	1.3	1.00	–
P ₇₅ –P ₈₉	12912	17.7	1.11 (1.03, 1.19)	0.0062	12.7	1.08 (1.01, 1.17)	0.0291	1.3	1.13 (0.91, 1.39)	0.2628
P ₉₀ –P ₉₄	5227	19.9	1.27 (1.16, 1.40)	<0.0001	13.8	1.33 (1.21, 1.47)	<0.0001	1.7	1.55 (1.20, 2.02)	0.0010
P ₉₅ –P ₉₆	2242	21.7	1.42 (1.24, 1.63)	<0.0001	15.0	1.45 (1.26, 1.66)	<0.0001	1.2	1.34 (0.88, 2.06)	0.1770
≥ P ₉₇	6284	25.2	1.65 (1.51, 1.80)	<0.0001	15.5	1.84 (1.68, 2.02)	<0.0001	1.2	1.34 (1.01, 1.78)	0.0402

^aAll estimates were based on two-level logistic regression models. Facilities represent units at level two and individuals within facilities are observations at level one. We adjusted for country, maternal age, marital status, education (total years of school attendance), obesity, diabetes, parity, infant sex and gestational age

America, respectively. The rise in PMMI risks lagged behind that of MMMI in all three regions (Fig. 2). The aORs of PMMI reached 2.0 when birthweight was greater than 4200 g in Asia and 5000 g in Africa. In Latin America, birthweight of 4500–4999 g corresponded to the aOR of PMMI 1.78 (95 % CI: 1.16, 2.74).

When birthweight was greater than 5000 g, aOR rose dramatically to 7.40 (95 % CI: 3.5, 15.66) (Table 4).

When we excluded prelabor caesarean deliveries or restricted the analyses to vaginal deliveries, the results remained essentially unchanged (Additional file 3: Tables S3 and S4).

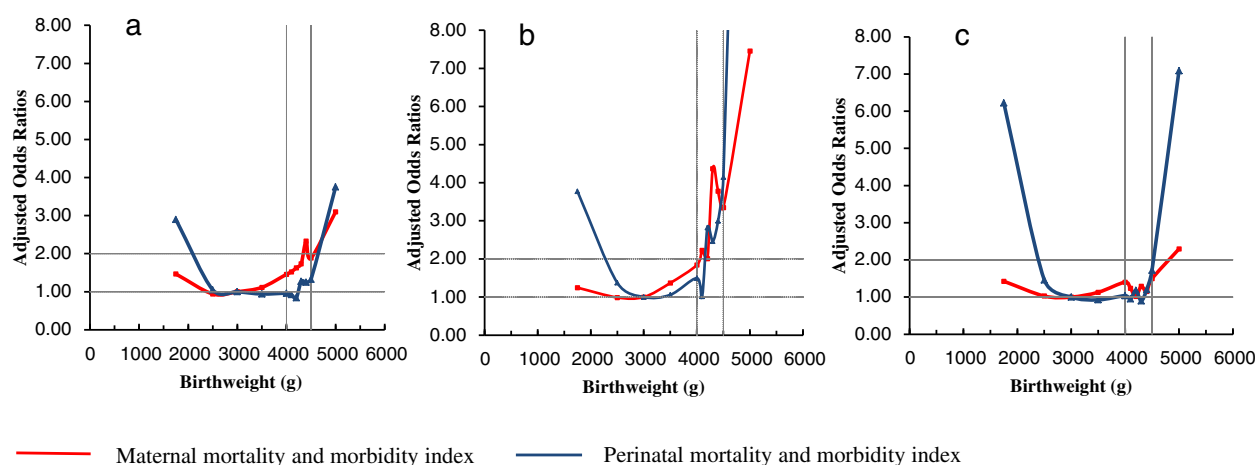


Fig. 2 Adjusted odds ratios of maternal and perinatal mortality and morbidity by birthweight in singleton term births. **a:** Africa **b:** Asia **c:** Latin America reference category: 3000–3499 g

Table 4 Prevalence and odds ratios of maternal and perinatal mortality and morbidity by birthweight

Birthweight (g)	N	Maternal mortality and morbidity			Perinatal mortality and morbidity		
		Prevalence (%)	Adjusted OR (95 % CI) ^a	p value	Prevalence (%)	Adjusted OR (95 % CI) ^a	p value
Africa	67546		N = 67546				
3000–3499	28788	6.0	1.00	–	4.6	1.00	–
3500–3999	15824	7.2	1.10 (1.01, 1.20)	0.0289	4.2	0.94 (0.85, 1.05)	0.2718
4000–4099	2154	9.1	1.43 (1.20, 1.70)	0.0001	4.0	0.97 (0.76, 1.23)	0.7780
4100–4199	670	10.6	1.48 (1.12, 1.96)	0.0061	3.4	0.93 (0.60, 1.44)	0.7424
4200–4299	686	11.7	1.59 (1.22, 2.07)	0.0006	3.4	0.84 (0.55, 1.31)	0.4473
4300–4399	377	14.3	1.68 (1.21, 2.34)	0.0021	5.0	1.29 (0.79, 2.09)	0.3122
4400–4499	239	15.5	2.26 (1.51, 3.39)	0.0001	3.8	1.26 (0.63, 2.49)	0.5147
4500–4999	648	15.0	1.84 (1.44, 2.36)	<0.0001	5.4	1.34 (0.93, 1.93)	0.1216
≥ 5000	146	21.2	3.01 (1.91, 4.74)	<0.0001	14.4	3.79 (2.28, 6.30)	<0.0001
Asia	91595		N = 91595				
3000–3499	36479	4.7	1.00	–	1.7	1.00	–
3500–3999	13539	5.4	1.38 (1.24, 1.52)	<0.0001	1.6	1.05 (0.90, 1.24)	0.5196
4000–4099	945	5.4	1.86 (1.35, 2.56)	0.0002	2.1	1.49 (0.94, 2.35)	0.0891
4100–4199	492	6.7	2.25 (1.50, 3.38)	0.0001	1.2	1.01 (0.45, 2.29)	0.9812
4200–4299	320	5.0	2.03 (1.17, 3.52)	0.0122	4.1	2.80 (1.58, 4.99)	0.0005
4300–4399	183	11.5	4.42 (2.60, 7.50)	<0.0001	3.3	2.44 (1.06, 5.64)	0.0366
4400–4499	101	7.9	3.81 (1.68, 8.60)	0.0013	4.0	2.99 (1.07, 8.34)	0.0367
4500–4999	200	10.0	3.38 (1.99, 5.74)	<0.0001	6.0	4.12 (2.24, 7.56)	<0.0001
≥ 5000	52	17.3	7.51 (3.25, 17.33)	<0.0001	26.9	28.44 (14.81, 54.61)	<0.0001
Latin America	87518		N = 87518				
3000–3499	38930	2.4	1.00	–	2.1	1.00	–
3500–3999	20875	2.6	1.15 (1.03, 1.28)	0.0157	2.0	0.94 (0.83, 1.06)	0.3390
4000–4099	1675	3.0	1.44 (1.08, 1.94)	0.0145	2.3	1.07 (0.77, 1.49)	0.6852
4100–4199	1020	2.6	1.28 (0.86, 1.90)	0.2229	2.2	0.98 (0.64, 1.52)	0.9422
4200–4299	757	2.5	1.05 (0.65, 1.70)	0.8450	2.8	1.22 (0.78, 1.91)	0.3719
4300–4399	466	3.0	1.34 (0.77, 2.31)	0.3014	2.1	0.94 (0.5, 1.77)	0.8429
4400–4499	281	2.8	1.19 (0.58, 2.46)	0.6381	2.8	1.25 (0.61, 2.56)	0.5378
4500–4999	569	3.5	1.54 (0.96, 2.45)	0.0708	4.0	1.78 (1.16, 2.74)	0.0089
≥ 5000	55	5.5	2.36 (0.70, 8.00)	0.1671	16.4	7.40 (3.50, 15.66)	<0.0001

^aAll estimates were based on two-level logistic regression models. Facilities represent units at level two and individuals within facilities are observations at level one. We adjusted for country, maternal age, marital status, education (total years of school attendance), obesity, diabetes, parity, infant sex, and gestational age

Table 5 shows that the risks of MMMI and PMMI in infants with a birthweight greater than the 95th percentile increased slightly compared with that of birthweight at the 50th–75th percentiles in all three regions. When birthweight was at the 97th percentile or higher, the aORs of MMMI and PMMI increased significantly, but none exceeded 2.0 in any region. In addition to the equation-derived global reference birthweight percentiles, we also used the empirical country- and gestational-age-specific birthweight percentile of the study population as cut-off points. The results were essentially unchanged (not shown).

We conducted sensitivity analyses using mortality and morbidity as two separate outcomes. The mortality included maternal and perinatal deaths. For morbidity, the occurrence of any components of MMMI and PMMI (excluding maternal or perinatal death) was considered as a positive event. As maternal and perinatal mortality were rare, no significant differences in mortality were found in the subgroups of infants with a birthweight greater than 4500 g, or the 97th birthweight percentile compared with the reference groups. However, results were similar for maternal and perinatal morbidity after excluding maternal or perinatal death (data not shown).

Table 5 Prevalence and odds ratios of maternal and perinatal mortality and morbidity by birthweight percentile

Birthweight percentile	N	Maternal mortality and morbidity			Perinatal mortality and morbidity		
		Prevalence (%)	Adjusted OR (95 % CI) ^a	<i>p</i> value	Prevalence (%)	Adjusted OR (95 % CI) ^a	<i>p</i> value
Africa	67546						
P ₅₀ –P ₇₄	15747	6.3	1.00	–	4.3	1.00	–
P ₇₅ –P ₈₉	10150	6.6	1.17 (1.05, 1.31)	0.0056	4.3	0.98 (0.86, 1.11)	0.7055
P ₉₀ –P ₉₄	5247	5.7	1.07 (0.93, 1.24)	0.3383	5.0	1.07 (0.92, 1.25)	0.3900
P ₉₅ –P ₉₆	1820	6.6	1.31 (1.05, 1.62)	0.0144	5.4	1.15 (0.91, 1.45)	0.2301
≥ P ₉₇	6851	7.2	1.54 (1.36, 1.75)	<0.0001	5.8	1.10 (0.96, 1.26)	0.1794
Asia	91595						
P ₅₀ –P ₇₄	18066	5.0	1.00	–	1.8	1.00	–
P ₇₅ –P ₈₉	14694	5.1	1.03 (0.92, 1.15)	0.5834	2.0	1.02 (0.86, 1.19)	0.8529
P ₉₀ –P ₉₄	5955	4.8	1.04 (0.89, 1.21)	0.6389	1.7	0.88 (0.70, 1.11)	0.2784
P ₉₅ –P ₉₆	3030	5.1	1.20 (0.98, 1.46)	0.0742	2.4	1.08 (0.83, 1.41)	0.5513
≥ P ₉₇	9574	6.4	1.41 (1.25, 1.59)	<0.0001	2.5	1.12 (0.94, 1.34)	0.1909
Latin America	87518						
P ₅₀ –P ₇₄	20003	2.4	1.00	–	2.0	1.00	–
P ₇₅ –P ₈₉	12912	2.7	1.13 (0.98, 1.30)	0.1014	2.2	1.10 (0.94, 1.29)	0.2236
P ₉₀ –P ₉₄	5227	2.6	1.06 (0.87, 1.29)	0.5709	1.8	0.89 (0.71, 1.12)	0.3257
P ₉₅ –P ₉₆	2242	2.9	1.21 (0.92, 1.58)	0.1744	2.1	0.98 (0.72, 1.34)	0.9162
≥ P ₉₇	6284	3.0	1.23 (1.03, 1.47)	0.0215	2.8	1.31 (1.09, 1.58)	0.0042

^aAll estimates based on two-level logistic regression models. Facilities represent units at level two and individuals within facilities are observations at level one. We adjusted for country, maternal age, marital status, education (total years of school attendance), obesity, diabetes, parity, infant sex, and gestational age

Similar trends for the risks of MMMI and PMMI by birthweight and birthweight percentile were found when we restricted the analyses to countries with less than 10 % of missing value for BMI (Additional file 3: Tables S5 and S6). When maternal obesity and diabetes were excluded from the regression models, aORs became larger for most of the subgroups, but the patterns remained the same in the three regions (Additional file 3: Tables S7 and S8).

Discussion

Our results indicate that there is a significant increase in adverse maternal and perinatal outcomes when the birthweight of term infants (37–42 weeks) reaches 4500 g in African and Latin America, and 4000 g in Asia. These cut-offs could, therefore, be used to define ‘macrosomia’ in these settings. Our findings do not support using LGA as a new definition for macrosomia because LGA was less predictive of adverse outcomes.

The use of the cut-off point of 4500 g to define macrosomia is consistent with results of previous studies of Caucasians populations [1, 9], and supports the definition of the American Congress of Obstetricians and Gynecologists [1]. Based on analyses of national datasets of the United States, Zhang et al. [7], found that infants with birthweight of 4500–4999 g were at significantly increased risks of stillbirth, neonatal mortality (especially

because of birth asphyxia), morbidity, and caesarean delivery as a consequence of either slow labor progress or non-reassuring cardiotocography. Ye et al. [9] used the same database also found that risks of MMMI or PMMI did not increased significantly until birthweight was at the 97th percentile or higher. A birthweight cut-off points irrespective of gestational age (4500 g in Whites, 4300 g in Blacks and Hispanics) is more predictive of mortality and morbidity outcomes than the 97th percentile for a given gestational age.

We used an OR of 2.0 for either MMMI or PMMI as *a priori* criterion to identify clinically important macrosomia. Though arbitrary, this cut-off point was also used in a study by Boulet et al. [18] in defining clinically important fetal growth restriction. In the randomized trial of the Twin Birth Study Collaborative Group, a relative risk of 0.5 was also used to justify the smallest clinically important difference between the planned caesarean delivery group and control group [19], equivalent to two-fold increase (or decrease) of risks.

Using the concept of birthweight percentile at a given gestational age (i.e., LGA) as the definition of macrosomia has been proposed in recent years [2, 10, 21]. However, our study shows that it has a poor prediction of adverse maternal and perinatal outcomes. This may be partially attributable to the imprecise estimation of gestational age, which has resulted in misclassifications of

macrosomia. Thus, a definition based on birthweight would be more practical, especially in settings where accurate estimation of gestational age may be difficult.

We observed that risks of elective and intrapartum caesarean section increased significantly for infants with a birthweight greater than 4000 g in the selected facilities of all three regions. However, the risks of or vacuum extraction did not increase prominently, which suggested that obstetricians may have a tendency for operative delivery when faced with a suspiciously large fetus and slow labor progress. Therefore, an estimated birthweight of 4000 g may be a useful indicator for difficult labour. We also found that risks of MMMI and PMMI did not change substantially after excluding elective caesarean deliveries, suggesting that suspected macrosomic cases may not benefit from elective caesarean section in a meaningful way. This was also demonstrated in other studies [22, 23].

We also observed that risks of MMMI increased prior to that of PMMI in three regions. This was consistent with the three-level definition of macrosomia proposed by Boulet et al. [3]: Grade 1 (>4000 g) to identify increased risks of labour and newborn complications; Grade 2 (>4500 g) to predict neonatal morbidity; and Grade 3 (>5000 g) to predict infant mortality. The major causes of maternal mortality and morbidity for mothers of macrosomic babies included uterine atony, prolonged labour, haemorrhage, vesico-vaginal/recto-vaginal fistula and severe perineal laceration [21]. These complications contributed to MMMI in our study. The most frequently severe adverse outcome was admission to an intensive-care unit (5.0 %), followed by blood transfusion (2.0 %) and third or fourth degree perineal laceration (1.5 %) for suspected macrosomia infants.

Macrosomia represents a significant obstetric challenge. The definition of macrosomia has important clinical, medico-legal and cost implications. Therefore, it should be evidence-based, particularly in resource limited countries where skilled birth attendants and caesarean delivery may not be readily available, and hospital transfer and special care are costly. To the best of our knowledge, this is the first study to search for an evidence-based definition of macrosomia in LMICs.

However, our study has several limitations. First, the significance of the definition of macrosomia using birthweight cut-off point in obstetric management is limited by the inaccuracy in birthweight estimation. Either ultrasound or clinical prediction of birthweight is not accurate enough to serve as the basis for obstetric decision making. But obstetricians are prone to operative delivery when faced with a suspected large fetus, which may lead to unnecessary cesarean [24].

Second, despite the standardization of data collection, participating facilities may have different labour

management protocols. Inter-institutional variability is inevitable due to the nature of a multinational study. For example, screening for diabetes in pregnancy is not available in all facilities, particularly in Africa [2], and therefore underestimation of gestational diabetes is likely. However, our sensitivity analysis, which excluded the variable “diabetes” from the regression models, showed a similar result to that of the fully adjusted models.

Third, information on maternal height and weight was problematic in two aspects. More than 10 % of data for height and/or weight were missing for some countries. In addition, maternal weight was defined differently across regions: in Africa and Latin America it was referred to as the first recorded weight at the first antenatal care visit while in Asia it was defined as the last recorded weight before delivery. In theory, the last recorded maternal weight would better control for the potential confounding effects of gestational weight gain in Asia [25]. However, the results of the sensitivity analysis, which excluded those countries or the variable “obesity” from the regression model indicated that the limitation did not affect the conclusion.

Finally, the sample used in the survey was selected from facilities with more than 1000 deliveries per year and where caesarean sections were available [11]. Selection bias is possible, especially in certain LMICs where an institutional delivery rate is low. Therefore, the generalizability of our findings may be limited.

Conclusions

A population-specific definition of macrosomia using birthweight cut-off points (4500 g in Africa and Latin America, 4000 g in Asia) for term infants at 37–42 gestational weeks is more closely associated with maternal and perinatal mortality and morbidity. This definition is also easier to apply than that based on birthweight percentile for a given gestational age. The use of an evidence-based definition of macrosomia may improve obstetric and perinatal care, especially in resource-limited settings in LMICs.

Additional files

Additional file 1: Table S1. Maternal characteristics by region and birthweight in singleton term births. (PDF 365 kb)

Additional file 2: Table S2. Indications for caesarean section in suspected macrosomic infants. (PDF 187 kb)

Additional file 3: Tables S3–S8. Results of sensitivity analyses. (PDF 577 kb)

Abbreviations

aORs: adjusted odds ratios; BMI: body mass index; ICU: intensive-care unit; LGA: large-for-gestational-age; LMICs: low- and middle-income countries; MMMI: maternal mortality and morbidity index; ORs: odds ratios; PMMI: perinatal mortality and morbidity index.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JFY and JZ participated in the study design. JFY analyzed the data and drafted the manuscript. JZ co-wrote the paper. MRT, EO, KJ, CP, EOP, PL, NM, ML, RM, ÖT, FF, HY, JPS, JPV provided critical comments and valuable suggestions on the manuscript. All authors contributed to the discussion, read and approved the final version of the manuscript.

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Review

Chicken Essence for Cognitive Function Improvement: A Systematic Review and Meta-Analysis

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Abstract: Chicken essence (CE) is a popular traditional remedy in Asia, which is believed to improve cognitive functions. CE company claimed that the health benefits were proven with research studies. A systematic review was conducted to determine the cognitive-enhancing effects of CE. We systematically searched a number of databases for randomized controlled trials with human subjects consuming CE and cognitive tests involved. Cochrane's Risk of Bias (ROB) tool was used to assess the quality of trials and meta-analysis was performed. Seven trials were included, where six healthy subjects and one subject with poorer cognitive functions were recruited. One trial had unclear ROB while the rest had high ROB. For executive function tests, there was a significant difference favoring CE (pooled standardized mean difference (SMD) of -0.55 (-1.04 , -0.06)) and another with no significant difference (pooled SMD of 0.70 (-0.001 , 1.40)). For short-term memory tests, no significant difference was found (pooled SMD of 0.63 (-0.16 , 1.42)). Currently, there is a lack of convincing evidence to show a cognitive enhancing effect of CE.

Keywords: chicken essence; chicken extract; cognitive function; executive function; attention; nutritional product; supplement; health claims

1. Introduction

Chicken essence (CE) is the cooked, concentrated, liquid extract from chicken, which is a popular traditional remedy amongst Asians [1–6]. In general, CE consists of major components of dipeptides and free amino acids, where carnosine and anserine are the most concentrated active ingredients [7,8]. Despite having a number of different CE companies in the market, the only variation found between commercial CE preparations is either with [9,10] or without [11,12] the addition of caramel as coloring agent. Combinational CE preparations are also commonly available, for example, with the addition of ginseng, cordyceps, or dong quai [10–12].

Over the past 20 years, CE company has claimed that the health benefits of CE are scientifically proven, with support from research conducted in Asia and the UK [9]. Promising results were reported in

research in terms of improvements in cognitive functions [2], mental fatigue [13], and mood [5], although most of these studies were sponsored by CE companies. The marketing of CE focused on consumers intend to improve cognitive functions, as well as stress and fatigue, immunity, and general well-being [9–12].

In recent year, an animal study [7] found that oral administration of CE to rats increased the concentration of carnosine and anserine in the brain. However, there was no clear indication how this can affect cognitive functions in human beings. A literature review [1], funded by CE company, summarized all the general effects of CE. However, in the review, the authors did not critically appraise a specific effect of CE with a clear-cut research question [1].

A number of randomized controlled trials (RCTs) [2–5,13–15] have been conducted to investigate the effects of CE in cognitive function improvement. However, there is a lack of critical appraisal and summary of the effects of CE in improving cognitive functions. This systematic review aims to critically appraise and summarize all the available evidence to determine the effects of CE in improving cognitive functions as well as its safety.

2. Materials and Methods

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) [16].

2.1. Protocol and Registration

The review protocol is registered with PROSPERO (registration number: CRD42015023474).

2.2. Data Sources and Search Strategy

We electronically searched for relevant articles published from inception to 30 September 2015. We searched MEDLINE, EMBASE, CINAHL Plus, Cochrane Central Register of Controlled Trials (CENTRAL), AMED (The Allied and Complementary Medicine Database), KoreaMed as well as local Chinese and Thai databases. Keywords used were chicken essence, chicken extract or chicken meat ingredients, and brain, cognition, memory, attention, analysis, or mathematics. There was no language restriction. In addition, bibliographies of relevant articles were examined to identify potential studies not indexed in aforementioned databases. Authors of relevant articles were enquired if they were aware of other relevant published or unpublished studies.

2.3. Study Selection

Studies were included if they were RCTs involving human subjects. The RCTs included were those which used chicken essence (CE) in the intervention group compared to at least one comparator. Test to assess cognitive functions must be employed in the RCTs. Studies included must provide adequate information related to the cognitive effects of CE, and study characteristics for data extraction. In the context of this review, cognitive effect refers to any domain of memory, language, attention, executive function, and information processing speed [17]. Studies were screened by two independent reviewers (SLT and SS). Initially, title and abstract of articles were screened to identify potentially relevant studies. Thereafter, full-text of relevant studies were retrieved and reviewed.

2.4. Data Extraction

Characteristics and results of trials were extracted by two independent reviewers (SLT and SS) using a standardized data extraction sheet. Any disagreement was resolved by discussion. Study designs, blinding status, characteristics of subjects, chicken essence, comparator, cognitive function test, duration of intake, interval of assessment, and funding status were extracted.

The characteristics extracted for cognitive function tests were the name of the cognitive function test, cognitive function domain, outcome measure and scale employed. The cognitive function domain was determined by understanding the procedure of each test. Each test was categorized into one

domain which is the primary domain, to prevent overweighing on one test and to enable consistent analysis throughout the review [18]. The outcome measurement of the cognitive function test was the primary outcome of interest. In addition, the adverse effects such as thirst and decreased bowel movements reported in the trials were the secondary outcome of interest. Data not available was requested directly by the corresponding author.

2.5. Study Quality Assessment

The methodological quality of each trial was assessed by two independent reviewers (SLT and SS) using a risk of bias (ROB) tool [19]. The domains for methodological evaluation using ROB tool include sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias [19]. The funding of the trials was assessed in the domain of “other sources of bias”. Each trial was classified as having low risk (low risk of bias for all domains), high risk (high risk of bias for one or more domains), or unclear risk (unclear risk of bias for one or more key domains, given no high risk of bias in any domain). In addition, Jadad score was determined for each trial by assessing randomization, double-blinding, and the account of all subjects [20].

2.6. Data Analysis

To determine the cognitive effect of CE, data of individual cognitive function tests were compared between CE group and comparator group using mean difference (MD) with 95% confidence interval (CI). Cognitive function tests with the same name, domain, outcome measure, and scale were pooled using weighted mean difference (WMD). Cognitive function tests with the same domain, outcome measure and scale, albeit with different names, were pooled using standardised mean difference (SMD). Heterogeneity of the included trial cognitive function tests was assessed using chi-squared test and I^2 test. Chi-squared test p-value of 0.10 or less indicates statistical significance of heterogeneity [19]. I^2 value of more than 50% indicates substantial heterogeneity [19]. Data from trials were pooled in a meta-analysis using a random-effects model [21] with 95% CI. The software used for data analysis was STATA[®] version 12 (STATA Corp, College Station, TX, USA).

2.7. Quality of Evidence

The overall quality of evidence was assessed using Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [22] that considered study design, ROB of individual trials, heterogeneity, directness of evidence, precision of effect estimates, and possibility of publication bias [22]. GRADEpro[®] version 3.6.1 (McMaster University, Hamilton, ON, Canada, 2014) software was used to generate the summary of findings (SoF) table. The overall quality of evidence ranged from high, moderate, low, to very low quality where high quality indicates the estimated effect lies close to the true effect while very low quality indicates the estimated effect is likely to be substantially different from the true effect [22].

2.8. Sensitivity Analysis

To ensure robustness of results, sensitivity analysis was performed by (1) meta-analysis using a fixed-effect model when there is no heterogeneity [23]; and (2) excluding data of trials with low quality from the meta-analysis.

3. Results

3.1. Study Selection

Our search yielded a total of 2870 potential articles including 2866 from electronic databases, two from bibliographies of relevant articles, and two from contacting authors. Six hundred and sixty-seven duplicates were removed. Of the remaining 2203 studies screened, only 13 were relevant and were

retrieved to be reviewed in full-text. During the full-text screening, only seven studies met the inclusion criteria. The six excluded studies either were non-RCT ($n = 4$), did not employ a cognitive function test ($n = 1$), and had inadequate information for data extraction ($n = 1$). As a result, a total of seven trials involving a total of 363 participants were included in this review. The trials were conducted in Malaysia [2,14,15], Japan [3,4,13], and United Kingdom [5]. The flow of study selection was shown in Figure 1.

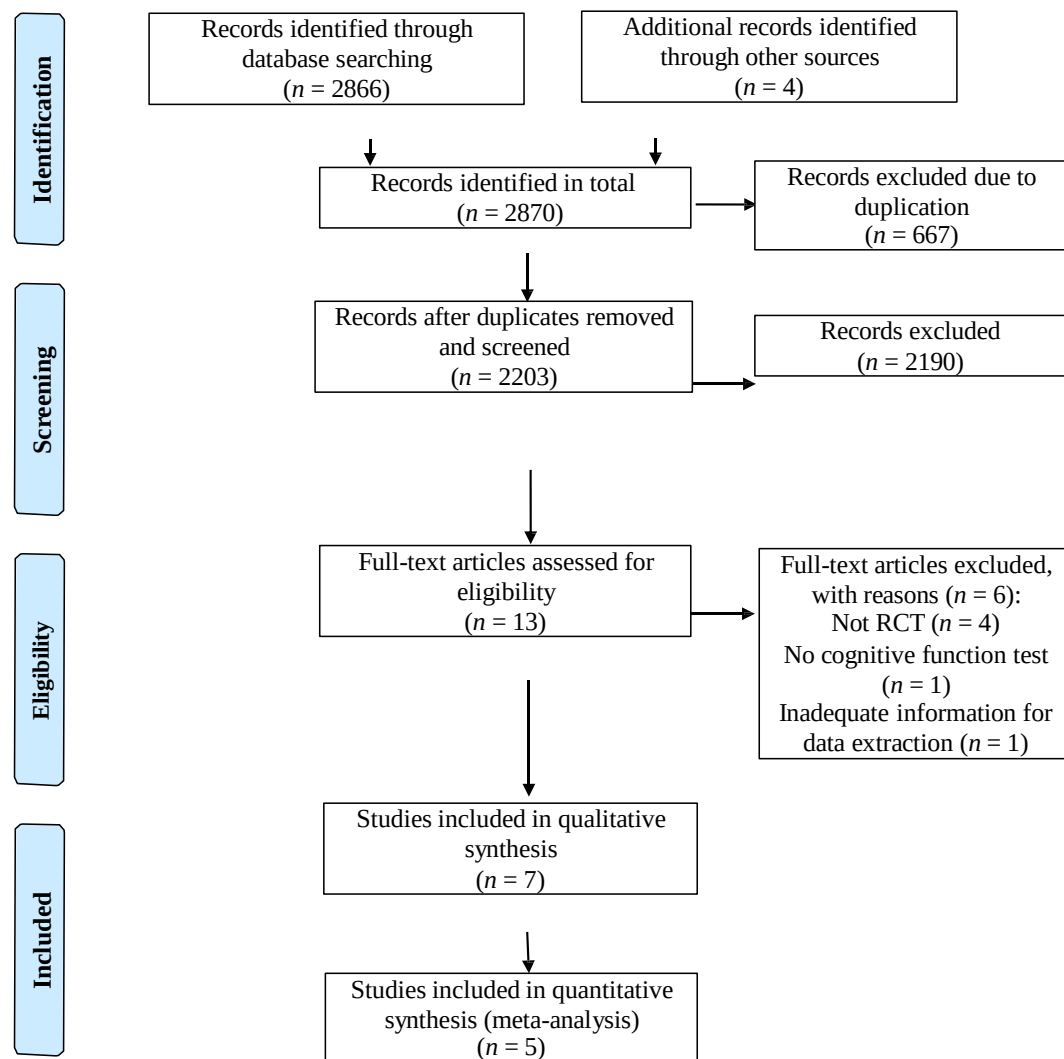


Figure 1. Flow of study selection.

3.2. Study Characteristics

The study characteristics were summarized in Table 1. Out of the seven trials, four [2,5,14,15] employed parallel design, and three [3,4,13] employed cross-over design. Out of the three trials, two [4,13] employed paired-analysis and only one [4] mentioned that a within-subject comparison was performed. The trial [3] which employed unpaired analysis did not mention whether the first or second period of cross-over trial was used for analysis. The study designs of the cross-over trials were summarized in Table 2.

Table 1. Study characteristics of included trials.

Author	RCT Design	Blinding Status (Stated by Author)	No. of Participants (Chicken Essence Group) ITT; Completed	No. of Participants (Placebo Group) ITT; Completed	Participants' Condition	Participants' Age Mean (Range)	Chicken Essence and Placebo's Form	Placebo	Test to Check Placebo's Similarity	Quantity	Intake Duration (Days)	Interval Assessed (Days)	Risk of Bias; Jadad Score
Nagai 1996, [4]	Cross-over	-	Total = 20; 16 #		Healthy volunteer	21.1 (18–24)	Liquid ~	Gelatin, caramel	-	140 mL	7	0,7	High; 1
Azhar 2003, [14]	Parallel	Double-blinded	60; 56	57; 52	Healthy volunteer §	—(23–24)	Liquid	Water, caramel	-	70 mL	14	0, 14	High; 1
Azhar 2008, [15]	Parallel	Double-blinded	Total ITT= 102 ‘; 38; 31		Healthy volunteer §	23 (22–24)	Liquid	Milk protein	-	70 mL	14	0, 14	High; 1
Azhar 2013, [2] ^	Parallel	Double-blinded	Total ITT= 46 ‘; 10; 10		Walk-in or general practitioner referred patients with poorer cognitive function	47.5 (35–65)	Tablet *	Microcrystalline cellulose	-	670 mg	42	0, 42, 56	High; 2
Konagai 2013, [3]	Cross-over	Double-blinded	Total = 12; 12 #		Healthy, elderly volunteer	62.3 (60–68)	Liquid *	Milk casein, caramel	-	140 mL	7	0,7	High; 1
Yamano 2013, [13] ^	Cross-over	-	Total = 20; 20 #		Healthy volunteer, male	34.7 (33–35)	Liquid *	Milk casein, caramel	-	140 mL	28	0, 7, 28	High; 1
Yamano 2015, [5] ^	Parallel	Double-blinded	24; 24	22; 22	Healthy volunteer	21.5–22.2 (-)	Liquid *	Milk casein, caramel	Yes	70 mL	10	0, 10	Unclear; 3

RCT, Randomized controlled trial; ITT, Intention-to-treat; - Not reported; # Participants in each group not reported; ~Brands chicken essence (Cerebos Pacific Limited, Singapore) was used; § Subjects were considered as generally healthy subjects in this review, although they were claimed as stressed in the trials; ‘ Intention-to-treat sample size only reported as a whole and not in separate groups; ^ Study funded by Cerebos Pacific Limited, Singapore; * Both chicken essence and placebo were supplied by Cerebos Pacific Limited, Singapore.

Table 2. Study design of cross-over trials.

Author	Paired/Unpaired Analysis	For Paired Analysis, within-Subject Comparison Performed?	For Unpaired Analysis, First or Second Period Used?
Nagai 1996, [4]	Paired	Yes	Not applicable
Konagai 2013, [3]	Unpaired	Not applicable	Not reported
Yamano 2013, [13]	Paired	Not reported	Not applicable

The total intention-to-treat number of subjects in each trial was relatively small, ranged from 20 [4] to 117 [14]. Subjects in the included trials were in the age-ranges of 18–24 [4,5,14,15], 33–35 [13], 35–65 [2], and 60–68 [3]. None of the trials assessed the effect of CE in children. Subjects in almost all (6/7) trials [3–5,13–15] were generally healthy. Although two trials [14,15] claimed that the subjects were in stressed condition, without stress level assessed, they were considered as generally healthy in this review. For one trial [2], the subjects were walk-in or general practitioner referred patients with poorer cognitive function.

All the included trials used placebo as the comparator. One trial [14] also used carrageenan as a comparator in addition to placebo. Almost all (6/7) trials [3–5,13–15] used liquid form of CE and comparators, while one trial [2] used tablet form. CE and placebo were supplied by a CE company (Cerebos Pacific Limited, Singapore) in four trials [2,3,5,13]. One trial [4] used Brand's® CE of Cerebos Pacific Limited, Singapore. Two trials [14,15] did not mention the source of the CE and comparators. The ingredients used for placebo in liquid form were mixture of milk casein and caramel [3,5,13], milk casein [15], water and caramel [14], and gelatin and caramel [4]. Placebo in tablet form of one trial [2] was made up of microcrystalline cellulose.

The quantity of CE and comparator in liquid administered for six trials were a daily dose of 70 mL [5,14,15] and 140 mL [3,4,13]. Three trials [3,5,13] quantified the active ingredients of CE, all of which were sourced from literature. CE in tablet of one trial [2] was administered with a daily dose of 670 mg, where the active ingredient was termed as “chicken meat ingredient-168”. The duration of intake varied from the range of seven days [3,4] the shortest to forty-two days [2] the longest. In addition to the assessment of cognitive functions after the last day of CE intake, one trial [2] also assessed the delayed-effect two weeks after discontinuing CE.

3.3. Study Quality Assessment

With assessment of quality using ROB tool, almost all (6/7) trials [2–4,13–15] were found to have overall high ROB. One trial [5] was found to have overall unclear ROB. ROB assessment for each domain was summarized in Table 3.

Table 3. Assessment of quality of trials using risk of bias (ROB) tool.

	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Reporting	Other Sources of Bias	Overall
Nagai 1996, [4]	High	Unclear	High	Low	Low	Unclear	High
Azhar 2003, [14]	Unclear	Unclear	High	Low	Low	Unclear	High
Azhar 2008, [15]	Unclear	Unclear	High	High	Low	Unclear	High
Azhar 2013, [2]	Unclear	Unclear	Unclear	High	High	High	High
Konagai 2013, [3]	Unclear	Unclear	High	Unclear	Low	High	High
Yamano 2013, [13]	Unclear	Unclear	High	Unclear	Low	Unclear	High
Yamano 2015, [5]	Unclear	Unclear	Unclear	Low	Low	Low	Unclear

Almost all (6/7) trials [2,3,5,13–15] were found to have unclear ROB for “sequence generation” domain. Even though “randomized” was mentioned in the six trials [2,3,5,13–15], there was no description of methods of sequence generation. One trial [4] was found to have high ROB for “sequence

generation” domain as the approach employed was non-randomized, where the allocation was determined by the result of a pre-arithmetic calculation test. All trials did not describe any component of “allocation concealment”.

For “blinding” domain, five trials [3,4,13–15] were found to have high ROB while two trials [2,5] had unclear ROB. The high ROB of blinding was because the liquid placebo used in the trials [3–5,13–15] could possibly have a different smell and taste from CE. In fact, taste difference between placebo and CE were documented in the trials [14,15]. Only one trial [5] conducted a test to check blinding of subjects.

For “incomplete outcome data” domain, three trials [4,5,14] were found to have low ROB as all withdrawal and dropouts were adequately reported with sound reasons, while two trials [3,13] were found to have unclear ROB as there was no description of withdrawal or dropouts. For the remaining two trials [2,15] with high ROB, one [15] had excluded around one-third (33/102) of the initial sample size for the final data synthesis in addition to incomplete reporting of (8/102) missing data, while another [2] had excluded more than half of the initial sample size (26/40). As for the “selective reporting” domain, one trial [2] was found to have high ROB as there was one pre-specified test outcome which was not reported. The remaining trials [3–5,13–15] were found to have low ROB for this domain.

For “other sources of bias” domain, three trials [2,5,13] clearly reported that they received funding from a CE company (Cerebos Pacific Limited, Singapore) while four trials [3,4,14,15] did not mention their source of funding. Of the three trials funded by the CE company, only one trial [5] was found to have low ROB as there was a declaration of no conflict of interest as the funding company was not involved in any part of the trial or manuscript preparation, besides the supply of CE and placebo. The other two trials [2,13] were found to have high ROB as the authors were affiliated with CE company and involved in trial design and conduct, data analysis, and manuscript preparation. The detailed assessment of ROB was summarized in Appendix A.

Jadad score was one for five trials [3,4,13–15], two for one trial [2], and three for one trial [5]. The assessment using Jadad scale was summarized in Table B1.

3.4. Effects of Chicken Essence in Cognitive Function Improvement

Of the seven included trials, 36 cognitive function outcome measurements were found where 30 had complete data available for data analysis. To ensure consistent comparison throughout the review, (1) data of carrageenan (comparator) group [14] and (2) data of delayed effect of CE [2] were not included in the analysis. Of the 30 complete data, 13 were found to have significant difference between CE group and placebo group, where eight were in executive function domain, and five in short-term memory domain. The detailed results of individual test were summarized in Table 4.

Outcome measures of the cognitive function tests employed in the seven included trials were oxy-hemoglobin concentration [3], score with scales of error [5], error rate [4], longest list of digits or/and words remembered [2,14,15], or with scale not reported [2,14,15], reaction time of decision and movement [5] or with scale not reported [5,13]. Data of oxy-hemoglobin concentration [3] was not pooled with others because we did not consider oxy-hemoglobin concentration a direct and validated measurement of cognitive function. Data of reaction time was not reported from one trial [13]. Consequently, five trials [2,4,5,14,15] were included for meta-analysis. Three pooled results were obtained from the meta-analysis, where two were in the executive function domain, and one in the short-term memory domain. Pooled results were summarized in Table 5. Forest plots of the three pooled results can be found in Figures C1–C3.

Table 4. Characteristics of cognitive function tests.

Cognitive Function Domain	Cognitive Function Test	Study	Outcome Measure (Scale)	Additional Information of Outcome Measure/Scale	Range of Score Reported	Mean Difference (95% CI)
Attention	Simple Reaction Task	Konagai 2013, [3]	Oxy-hemoglobin concentration (NA)	The presence of oxy-hemoglobin in brain during cognitive function test	NR	NR
	EE-Arrow Flankers Test (Congruent)	Yamano 2015, [5]	Score (Error) \$	Number of incorrect answer of cognitive function test	−2.8–1.3	−0.33 (−0.91, 0.26)
	EE-Arrow Flankers Test (Neutral)	Yamano 2015, [5]	Score (Error) \$	Number of incorrect answer of cognitive function test	−2.8–1.3	−0.24 (−0.82, 0.34)
	EE-Arrow Flankers Test (Incongruent)	Yamano 2015, [5]	Score (Error) \$	Number of incorrect answer of cognitive function test	−2.8–1.3	−0.47 (−1.06, 0.11)
	EE-Arrow Flankers Test (Congruent)	Yamano 2015, [5]	Reaction time (NR ~) \$	Time used to complete cognitive function test	470.9–1184.6	−0.001 (−0.58, 0.58)
	EE-Arrow Flankers Test (Neutral)	Yamano 2015, [5]	Reaction time (NR ~) \$	Time used to complete cognitive function test	470.9–1184.6	−0.10 (−0.68, 0.48)
	EE-Arrow Flankers Test (Incongruent)	Yamano 2015, [5]	Reaction time (NR ~) \$	Time used to complete cognitive function test	470.9–1184.6	0.13 (−0.45, 0.71)
	Jensen-Simple and Choice Reaction Time	Yamano 2015, [5]	Reaction time (Decision time ~) \$	Time used to complete cognitive function test	122.4–671.1	−0.36 (−0.92, 0.24)
Executive Function	Jensen-Simple and Choice Reaction Time	Yamano 2015, [5]	Reaction time (Movement time ~) \$	Time used to complete cognitive function test	132.1–661.8	−0.51 (−1.10, 0.08)
	Nagai's Mental Arithmetic Test	Nagai 1996, [4]	Score (Error rate) \$	Percentage of incorrect answer out of the filled answer	NR	−0.76 (−1.64, 0.12)
	The Three Minute Memory Test	Azhar 2003, [14]	Score (NR ~) \$	NR	1.1–8.7	0.16 (−0.22, 0.54)
	WAIS-Digit Span	Azhar 2003, [14]	Score (Longest list ~) \$	Longest list of digits remembered	11.3–32.7	0.23 (−0.15, 0.61)
	Mental Arithmetic Test	Azhar 2003, [14]	Score (NR ~) \$	NR	2.8–14.7	0.98 (0.34, 1.62) *
	WAIS-Arithmetic Test	Azhar 2008, [15]	Score (NR ~) \$	NR	9.6–26.8	0.73 (−1.27, 2.73) *
	WAIS-Digit Backward	Azhar 2008, [15]	Score (Longest list ~) \$	Longest list of digits remembered	5.2–10.7	0.47 (−0.57, 1.51)
	WAIS-Digit Backward	Azhar 2013, [2]	Score (Longest list ~) \$	Longest list of digits remembered	24.2–28.3	2.00 (1.14, 2.86) *
	Letter Number Sequencing	Azhar 2008, [15]	Score (Longest list ~) \$	Longest list of letters and digits remembered	8.9–16.1	0.31 (−0.17, 0.78)

Table 4. Cont.

Cognitive Function Domain	Cognitive Function Test	Study	Outcome Measure (Scale)	Additional Information of Outcome Measure/Scale	Range of Score Reported	Mean Difference (95% CI)
	Letter Number Sequencing	Azhar 2013, [2]	Score (Longest list ~) \$	Longest list of letters and digits remembered	17.2–19.6	6.25 (4.03, 8.47) *
	RAVLT-Delayed Recall	Azhar 2013, [2]	Score (Longest list ~) \$	Longest list of words remembered	17.7–6.4	3.33 (1.94, 4.73) *
	RAVLT-Recall	Azhar 2013, [2]	Score (Longest list ~) \$	Longest list of words remembered	6.6–17.7	2.81 (1.54, 4.08) *
	RAVLT-Retroactive Interference	Azhar 2013, [2]	Score (Longest list ~) \$	Longest list of words remembered	5.9–19.2	4.06 (2.47, 5.65) *
	Working Memory Test	Konagai 2013, [3]	Oxy-Hemoglobin Concentration (NA) \$	The presence of oxy-hemoglobin in brain during cognitive function test	NR	0.20 (0.06, 0.34) *
	Traffic Light's Test	Yamano 2013, [13]	Reaction time (NR ~)	Time used to complete cognitive function test	NR	NR
	Stroop Test	Yamano 2013, [13]	Reaction time (NR ~)	Time used to complete cognitive function test	NR	NR
	Serial Sevens	Yamano 2015, [5]	Score (Error) \$	Number of incorrect answer of cognitive function test, time used to complete cognitive function test	−3.8	−0.46 (−1.05, 0.13)
	Serial Sevens	Yamano 2015, [5]	Reaction time (NR ~) \$	Time used to complete cognitive function test	705.7–3032.9	0.32 (−0.27, 0.90)
Long-term Memory	Non-Stroop Test	Yamano 2013, [13]	Reaction time (NR ~)	Time used to complete cognitive function test	NR	NR
Short-term Memory	Short-term Memory Test	Nagai 1996 [4]	Score (Error rate)	Percentage of incorrect answer out of the filled answer	NR	NR
	Mental Comprehension Test	Azhar 2003, [14]	Score (NR ~) \$	NR	0.6–11.4	0.64 (0.25, 1.02) *
	WAIS-Digit Forward	Azhar 2008, [15]	Score (NR ~) \$	Longest list of digits remembered	8.4–20.7	−0.10 (−0.57, 0.37)
	RAVLT-Proactive Interference	Azhar 2013, [2]	Score (NR ~) \$	Longest list of words remembered	7.5–19.1	3.75 (2.24, 5.26) *
	RAVLT-Immediate Memory	Azhar 2013, [2]	Score (NR ~) \$	NR	8.0–20.4	3.92 (2.37, 5.47) *
	RAVLT-Best Learning	Azhar 2013, [2]	Score (NR ~) \$	NR	8.5–21.4	1.70 (0.66, 2.74) *
	RAVLT-Total Learning	Azhar 2013, [2]	Score (NR ~) \$	NR	43.8–105.6	6.50 (2.66, 10.34) *

Table 4. Cont.

Cognitive Function Domain	Cognitive Function Test	Study	Outcome Measure (Scale)	Additional Information of Outcome Measure/Scale	Range of Score Reported	Mean Difference (95% CI)
Visuospatial Skills	Figures Construction Test	Azhar 2003, [14]	Score (NR ~) \$	NR	1.2–7.9	0.28 (−0.10, 0.66)
	Milner and Snyder-Groton Maze Learning Test	Konagai 2013, [3]	Oxy-hemoglobin concentration (NA)	The presence of oxy-hemoglobin in brain during cognitive function test	NR	NR
(Subdomain) Information Processing Speed	Traffic Light's Test	Yamano 2013, [13]	Reaction time (NR ~)	Time used to complete cognitive function test	NR	NR
	Stroop Test	Yamano 2013, [13]	Reaction time (NR ~)	Time used to complete cognitive function test	NR	NR
	Non-Stroop Test	Yamano 2013, [13]	Reaction time (NR ~)	Time used to complete cognitive function test	NR	NR
	EE-Arrow Flankers Test (Congruent)	Yamano 2015, [5]	Reaction time (NR ~)	Time used to complete cognitive function test	470.9–1184.6	−0.00 (−0.58, 0.58)
	EE-Arrow Flankers Test (Neutral)	Yamano 2015, [5]	Reaction time (NR ~)	Time used to complete cognitive function test	470.9–1184.6	−0.10 (−0.68, 0.48)
	EE-Arrow Flankers Test (Incongruent)	Yamano 2015, [5]	Reaction time (NR ~)	Time used to complete cognitive function test	470.9–1184.6	0.13 (−0.45, 0.71)
	Jensen-Simple and Choice Reaction Time	Yamano 2015, [5]	Reaction time (Decision time ~) \$	Time used to complete cognitive function test	122.4–671.1	−0.36 (−0.92, 0.24)
	Jensen-Simple and Choice Reaction Time	Yamano 2015, [5]	Reaction time (Movement time ~) \$	Time used to complete cognitive function test	132.1–661.8	−0.51 (−1.10, 0.08)
	Serial Sevens	Yamano 2015, [5]	Reaction time (NR ~)	Time used to complete cognitive function test	705.7–3032.9	0.32 (−0.27, 0.90)

* Result with significant difference; NA, Not applicable; NR, Not reported; EE, Eriksen and Eriksen; \$ Result with complete data for analysis; ~ Result that followed the trend that higher score or shorter reaction time indicates better cognitive functions; WAIS, Wechsler Adult Intelligence Scale; RAVLT, Rey Auditory Verbal Learning Test.

Table 5. Pooled results of meta-analysis using a random-effects model.

Cognitive Area	Study	ROB	Test	Outcome Measure	Pooled SMD (95% CI)
Executive Functions	Nagai 1996, [4]	High	Nagai's Mental Arithmetic Test Serial Sevens	Score (Error rate)	−0.55 (−1.04, −0.06) * $I^2 = 0\%$, $p = 0.58$
	Yamano 2015, [5]	Unclear		Score (Error)	
	Azhar 2003, [14]	High	Digit Span Test	Score (Longest list)	0.70 (−0.001, 1.40) $I^2 = 77.7\%$, $p = 0.01$
	Azhar 2008, [15]	High	Digit Backward	Score (Longest list)	
	Azhar 2013, [2]	High	Digit Backward	Score (Longest list)	
Short-term Memory	Azhar 2003, [14]	High	Mental Comprehension Test	Score (NR ~)	0.63 (−0.16, 1.42) $I^2 = 82.9\%$, $p = 0.00$
	Azhar 2008, [15]	High	Digit Forward	Score (NR ~)	
	Azhar 2013, [2]	High	Best Learning β	Score (NR ~)	

ROB, Risk of bias; SMD, Standardized mean difference; CI, Confidence interval; * Result with significant difference; NR, Not reported; ~ Results that followed the trend that higher score or shorter reaction time indicates better cognitive functions; β Best Learning test was chosen from Azhar 2013, [2] because the range of reported score was the closest to the range of score of two other tests pooled together (as we did not know which scale was employed), and its standard deviation is the widest (*i.e.*, conservative estimate).

For executive function domain, we had included five trials [2,4,5,14,15] with 259 subjects in two separate analyses. For the first analysis, a significant pooled SMD of -0.55 (95% CI: $-1.04, -0.06$) with no heterogeneity ($I^2 = 0\%$, $p = 0.58$) was observed among two included trials [4,5] with 62 subjects. The score of error rate and error for executive function tests were pooled from two trials with high [4] and unclear ROB [5]. The scores were pooled, albeit with different scales, because they followed the trend where lower score indicates better cognitive functions. The data of the cross-over trial [4] were pooled with another trial [5] which was parallel [19].

For the second analysis of the executive function domain, a non-significant pooled SMD of 0.70 (95% CI: $-0.001, 1.40$) with substantial heterogeneity ($I^2 = 77.7\%$, $p = 0.01$) was obtained from the score with scale of longest list of digits of the three trials [2,14,15] with high ROB which involved 197 subjects. The substantial heterogeneity can possibly be explained by the difference of subjects in the trials. The sample in one of the trials [2] was older with an age-range of 35–65, and with poorer cognitive functions, whereas the subjects of the other two trials [14,15] were of the age-range of 22–24 and generally healthy. In addition, the regimens of CE administered were different where one trial [2] used CE in tablet form for a more prolonged period of 42 days compared to the two trials [14,15] which used CE in liquid form for a period of 14 days. When the trial [2] with different subject characteristics and CE regimen was removed, a significant pooled SMD of 0.35 (0.05, 0.65) with no heterogeneity ($I^2 = 0\%$, $p = 0.475$) was obtained; pooled SMD was not changed when fixed-effect model was used. The forest plot of the pooled result can be found in Figure D1.

For short-term memory domain, a non-significant pooled SMD of 0.63 ($-0.160, 1.42$) with substantial heterogeneity ($I^2 = 82.9\%$, $p = 0.001$) was obtained from the scores of three trials [2,14,15] with high ROB which involved 197 subjects. Although the scales employed in the three trials were not reported, the data were pooled as they followed the trend that higher score indicates better cognitive functions. We explored the causes of heterogeneity and could not identify the clear source. Further meta-analysis was performed by removing either one of three trials from the pooled results, all of which still produced substantial heterogeneity. The forest plots of the pooled result can be found in Figures D2–D4.

3.5. Adverse Effects

Adverse effects of consuming CE were assessed in two out of seven trials [2,5]. One trial [5] reported no significant difference between CE group and placebo group on the reported rates of thirst, decreased bowel movements, tiredness, and slight insomnia. No adverse effect was recorded in another trial [2].

3.6. Quality of Evidence

Using GRADE approach, the quality of evidence to recommend CE for improving executive functions was found to be either low or very low. The same scenario applied for recommendation of short-term memory where the quality of evidence was very low. The low quality of evidence was due to the reasons that (1) individual studies had low quality (high and unclear ROB); and (2) inconsistency of effect in cognitive functions improvement with substantial heterogeneity. Summary of findings (SoF) table was presented in Table 6.

3.7. Sensitivity Analysis

It was not possible to perform sensitivity analysis by excluding data of trials with low quality from the meta-analysis due to the reasons that (1) a limited number of trials were pooled and (2) all trials were of low quality (high or unclear ROB).

Table 6. Summary of findings (SoF) table for cognitive function outcomes of meta-analysis measured in clinical trials of chicken essence. §

Outcomes	Relative Effect (95% CI)	No of Participants (Studies)	Quality of the Evidence (GRADE)
Executive Functions Error Rate Follow-up: 7–10 days	The mean executive functions in the intervention groups was 0.55 standard deviations lower (1.04 to 0.06 lower)	62 (2 studies)	⊕⊕⊕⊖ low ¹
Executive Functions Performance Score Follow-up: 2–8 weeks	The mean executive functions in the intervention groups was 0.70 standard deviations higher (0.001 lower to 1.4 higher)	197 (3 studies)	⊕⊕⊕⊕ very low ^{2,3}
Short-term Memory Performance Score Follow-up: 2–8 weeks	The mean short-term memory in the intervention groups was 0.63 standard deviations higher (0.16 lower to 1.42 higher)	197 (3 studies)	⊕⊕⊕⊕ very low ^{2,4}

§ Among studies that compared chicken essence with placebo in healthy subjects and subjects with poorer cognitive functions. ¹ Both studies have unclear risk of bias; ² All 3 studies have high risk of bias; ³ Very high I^2 value of 77.7%; ⁴ Very high I^2 value of 82.9%. CI: Confidence interval. GRADE Working Group grades of evidence—**High quality**: Further research is very unlikely to change our confidence in the estimate of effect; **Moderate quality**: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; **Low quality**: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; **Very low quality**: We are very uncertain about the estimate.

4. Discussion

To the extent of our knowledge, this is the first systematic review which critically appraises and summarizes the available evidence about the effects of CE in improving cognitive functions. Based on a combination of cognitive function tests, the pooled effects were significant for some measures (in the executive function domain) and not significant for other measures (in the executive function and short-term memory domains). There were great uncertainties on the possible effect sizes, although it appeared that the effects, if present, were at best modest and non-clinically significant. Therefore, the overall findings need to be interpreted with caution.

The findings of our review was consistent with the RCTs [24,25] evaluating the effects of carnosine (the active ingredient of CE). The two RCTs which also employed a combination of cognitive function tests, in schizophrenia patients [24] and Persian Gulf War veterans [25], respectively, found that the effects were only significant for certain cognitive function tests but not all. The imminently inconclusive findings about the effect of cognitive properties of CE can be related to the methodological issues of cognitive function tests. Future RCTs intended to employ cognitive function tests should consider referring to guidance available [17,26] in order to make a sound selection of appropriate cognitive function tests.

A study report [26] proposed that the change of attention can contribute to relative change to other cognitive function domains. In our review, however, given the limited number of trials included, there was no summary of effect given for attention domain. With the findings of individual attention tests, all the results were insignificant. This could imply that any effect of CE on the executive function domain might not be due to the change of attention based on our review. However, more future RCTs should employ attention tests concurrently with tests assessing other cognitive function domains in order to justify this relationship.

As with any systematic review and meta-analysis, our review shares the limitations of the original trials. Firstly, the quality of included trials was low with high or unclear ROB. Secondly, cognitive function tests employed in the trials provided an ambiguous interpretation of cognitive-enhancing effects of CE. However, based on the most reasonably applicable methods employed to generate quantitative synthesis (meta-analysis), in addition to qualitative synthesis, this review provided important information about the direction of the cognitive-enhancing effects of CE and the designs and characteristics of the RCTs evaluating the cognitive functions of CE conducted so far. Lastly, although we have performed an exhaustive literature search, there might be unpublished study that we were unaware of. Due to the small number of trials included, publication bias was not tested. In a nutshell, the overall low and very low quality evidence based on GRADE indicates that a cautious interpretation of findings is warranted.

5. Conclusions

With the current evidence available, it is premature to support the claim that CE has cognitive-enhancing effects. More high quality RCTs are needed to better determine its effect.

Our review can potentially be used as information for healthcare-providers and the public to understand the current limited evidence of CE in supporting the claim of cognitive function improvement. Caution should be taken when interpreting health claims used for advertising nutritional products, especially in countries with a lack of a unified approach in the regulatory framework for health claims [27].

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A. Assessment of quality of trials using Risk of Bias (ROB) tool.

Table A1. Risk of bias assessment of Nagai 1996 [4].

Items	Judgement	Specifics
Sequence Generation	High	Quote: “according to a pre-arithmetic calculation test to equalize in both groups the abilities to perform tasks”. Comment: A non-random approach was employed. Review authors believe this can introduce bias.
Allocation Concealment	Unclear	There was no description of allocation concealment.
Blinding	High	Quote: “same appearance and caloric content” Comment: The smell and taste of the placebo can differ from chicken essence (CE). Review authors believe this can introduce bias.
Incomplete Outcome Data	Low	Quote: “4/20 dropouts. (refused to continue the test)” Comment: Review authors believe no bias was introduced.
Selective Reporting	Low	Review authors believe no bias was introduced as all the pre-specified outcomes were adequately reported.
Other sources of bias	Unclear	There was no mention of funding, or declaration of conflict of interest.
Overall	High	

Table A2. Risk of bias assessment of Azhar 2003, [14].

Items	Judgement	Specifics
Sequence Generation	Unclear	Quote: “subjects were randomly divided”. Comment: Method of sequence generation was not specified.
Allocation Concealment	Unclear	There was no description of allocation concealment.
Blinding	High	Quote: “double-blind”; “taste difference between test samples”; “all subjects had not previously taken CEC”; “Investigator 1 who conducted the tests were blinded to the samples”; “Investigator 2 kept a record of all the samples”. Comment: The smell and taste of the placebo can differ from CE. Review authors believe this can introduce bias.
Incomplete Outcome Data	Low	Quote: “5/57 dropouts in placebo group, 4/60 dropouts in CE group, 3/58 dropouts in carrageenan group (due to personal reasons, non-compliance); 1/176 missing data”. Comment: Review authors believe no bias was introduced.
Selective Reporting	Low	Review authors believe no bias was introduced as all the pre-specified outcomes were adequately reported.
Other sources of bias	Unclear	There was no mention of funding, or declaration of conflict of interest.
Overall	High	

Table A3. Risk of bias assessment of Azhar 2008, [15].

Items	Judgement	Specifics
Sequence Generation	Unclear	Quote: “subjects were randomly divided”. Comment: Method of sequence generation was not specified.
Allocation Concealment	Unclear	There was no description of allocation concealment.
Blinding	High	Quote: “double-blind”; “placebo made up of milk protein (casein), as a comparison test sample”; “potential taste differences”; “most subject had not taken CEC previously, those who had taken it more than 10 years ago indicated they have no significant recollections”; “Investigator 1 who conducted the tests were blinded to the samples”; “Investigator 2 maintained a record of all the samples”. Comment: The smell and taste of the placebo can differ from CE. Review authors believe this can introduce bias.
Incomplete Outcome Data	High	Quote: “25/102 excluded (due to technical errors); 8/102 missing data”. Comment: One-third of the initial sample size (33/102) was excluded. Review authors believe this can introduce bias.
Selective Reporting	Low	Review authors believe no bias was introduced as all the pre-specified outcomes were adequately reported.
Other sources of bias	Unclear	There was no mention of funding, or declaration of conflict of interest.
Overall	High	

Table A4. Risk of bias assessment of Azhar 2013, [2].

Items	Judgement	Specifics
Sequence Generation	Unclear	Quote: “subjects were randomly divided”. Comment: Method of sequence generation was not specified.
Allocation Concealment	Unclear	Quote: “investigator did not know their group allocation” Comment: Method of allocation concealment was not specified.
Blinding	Unclear	Quote: “double-blind”; “placebo tablets contain microcrystalline cellulose”; “Investigator who conducted the tests were blinded to the information about the group allocation and samples provided”; “Independent investigator who has no information about the assessment maintained the record of all the samples and group allocation”. Comment: It is unclear whether the placebo had similar appearance and taste as CE tablet. Hence it is unclear whether if the study design was single- or double-blinded.
Incomplete Outcome Data	High	Quote: 26/40 excluded from data analysis due to either non-compliance of supplementation or withdrawal from the study. Comment: More than half of the initial sample size (26/40) was excluded. Review authors believe this can introduce bias.
Selective Reporting	High	One of the outcomes (DS Forward test) as mentioned in protocol was not reported. Review authors believe this can introduce bias.
Other sources of bias	High	The trial clearly mentioned that it was funded by CE company. In addition, it was clearly mentioned that three of the authors were affiliated with CE company where they were involved with study conduct, data analysis, and preparation of the manuscript. Review author believes this can introduce bias.
Overall	High	

Table A5. Risk of bias assessment of Konagai 2013, [3].

Items	Judgement	Description
Sequence Generation	Unclear	Quote: “volunteers were divided randomly”. Comment: Method of sequence generation was not specified.
Allocation Concealment	Unclear	There was no description on allocation concealment.
Blinding	High	Quote: “double-blind”; “placebo contained milk casein, caramel, and flavoring to yield proteins, calories, and color similar to CE”; “no subjects had previously taken CE”. Comment: Even placebo was reported to be prepared in a way to have proteins, calories, and color similar to CEC, placebo can still have different taste and smell compared to CE. Review authors believe this can introduce bias.
Incomplete Outcome Data	Unclear	There was no description of dropouts or withdrawals.
Selective Reporting	Low	Review authors believe no bias was introduced as all the pre-specified outcomes were adequately reported.
Other sources of bias	High	Three authors were affiliated with CE company and there was no mention of funding, or declaration of conflict of interest. Review authors believe this can introduce bias.
Overall	High	

Table A6. Risk of bias assessment of Yamano 2013, [13].

Items	Judgement	Specifics
Sequence Generation	Unclear	Quote: “randomly assigned”. Comment: Method of sequence generation was not specified.
Allocation Concealment	Unclear	There was no description of allocation concealment.
Blinding	High	Quote: “protein content, caloric content and color similar to CE” Comment: Even placebo was reported to be prepared in a way to have proteins, calories, and color similar to CEC, placebo can still have different taste and smell compared to CE. Review authors believe this can introduce bias.
Incomplete Outcome Data	Unclear	There was no description of dropouts or withdrawals.
Selective Reporting	Low	Review authors believe no bias was introduced as all the pre-specified outcomes were adequately reported.
Other sources of bias	Unclear	The trial clearly mentioned that it was funded by CE company. In addition, it was clearly mentioned that two of the authors were affiliated with CE company where they were involved with study design and conduct, data analysis, and data interpretation. Review author believes this can introduce bias.
Overall	High	

Table A7. Risk of bias assessment of Yamano 2015, [5].

Items	Judgement	Specifics
Sequence Generation	Unclear	Quote: “randomly allocated” Comment: Method of sequence generation was not specified.
Allocation Concealment	Unclear	There was no description of allocation concealment.
Blinding	Unclear	Quote: “double-blind”, “blind was successful” Comment: Patients-blinding was checked by test. However, there was no description on the blinding of personnel and outcome assessors.
Incomplete Outcome Data	Low	Quote: “4/50 dropouts where 3 were in placebo arm and 1 in CE arm”. Comment: Review authors believe no bias was introduced.
Selective Reporting	Low	Review authors believe no bias was introduced as all the pre-specified outcomes were adequately reported.
Other sources of bias	Low	The study clearly mentioned it was funded by CE company. However, authors declared no conflict of interest where the funding sponsors had no role in study design, or any part of study design and conduct, or data analysis, or preparation and publication of the study. Review authors believe no risk was introduced.
Overall	Unclear	

Appendix B

Table B1. Assessment of quality of trials using Jadad scale.

Items	Nagai 1996, [4]	Azhar 2003	Azhar 2008	Azhar 2013	Konagai 2013, [3]	Yamano 2013	Young 2015
Was the study described as randomized?	0	1	1	1	1	1	1
Was the method used to generate the sequence of randomization described and appropriate?	0	0	0	0	0	0	0
Was the study described as double blind?	0	1	1	1	1	0	1
Was the method of double blinding described and appropriate?	0	0	0	0	0	0	0
Was there a description of withdrawals and dropouts?	1	0	0	1	0	0	1
Deduct 1 point if the method used to generate sequence of randomization was described and it was inappropriate.	0	0	0	0	0	0	0
Deduct 1 point if the study was described as double blind but the method of blinding was inappropriate.	0	−1	−1	−1	−1	0	0
Total Jadad scores	1	1	1	2	1	1	3

Appendix C. Pooled results using a random-effects model.

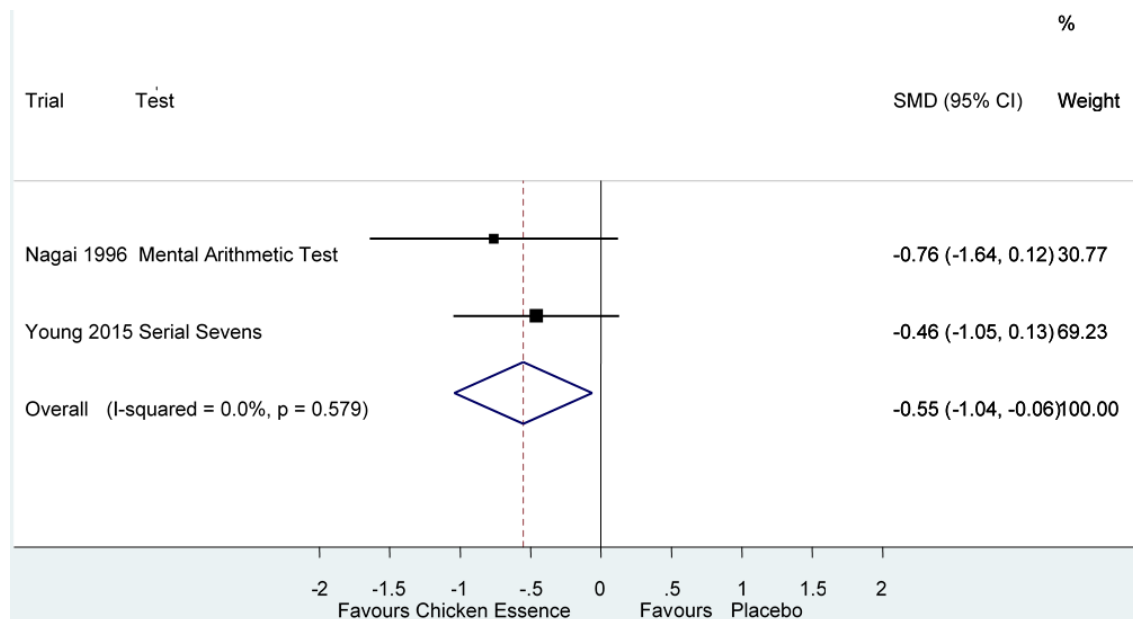


Figure C1. Pooled effect estimate of score of error and error rate of executive function tests. SMD, Standardized mean difference; CI, Confidence interval.

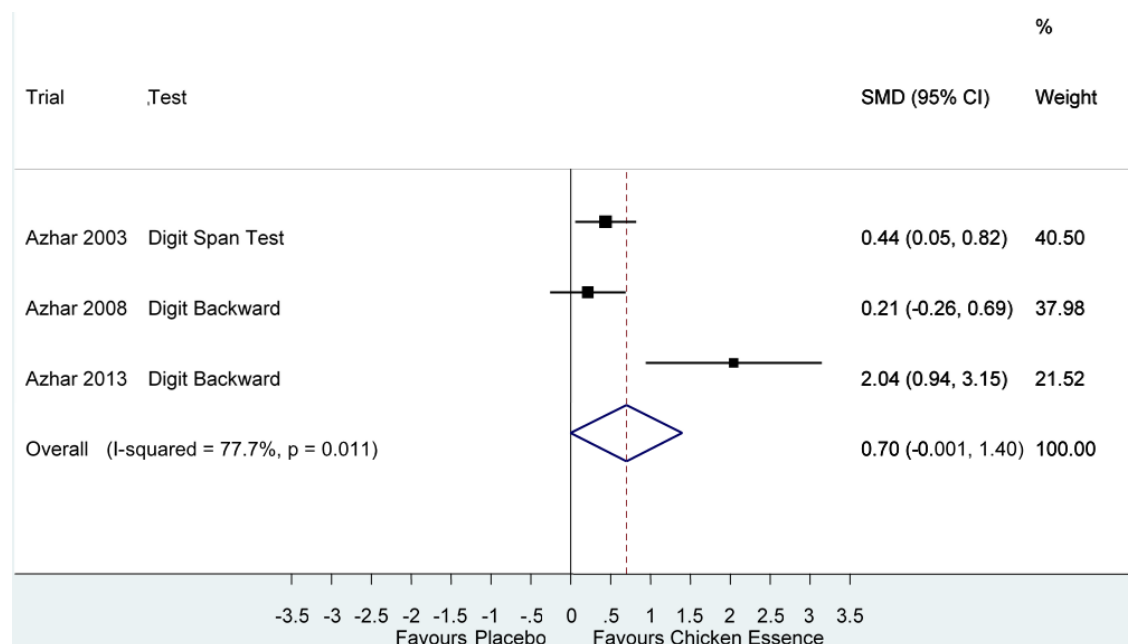


Figure C2. Pooled effect estimate of score of longest list of digits remembered of executive function tests.

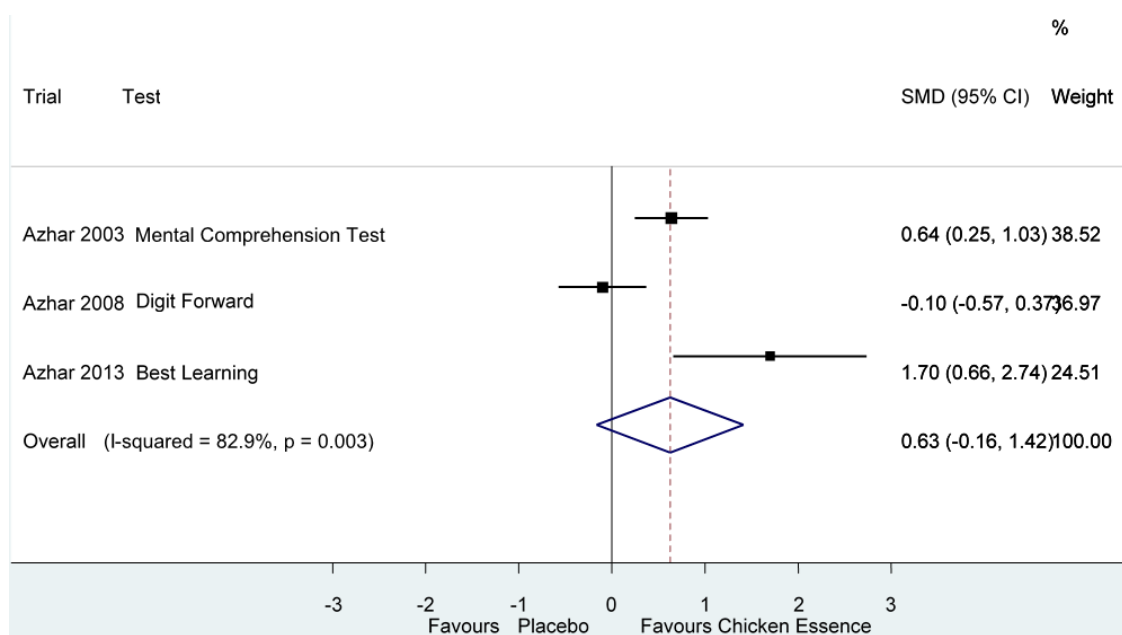


Figure C3. Pooled effect estimate of score of short-term memory tests.

Appendix D. Pooled results with removal of test which possibly caused heterogeneity.

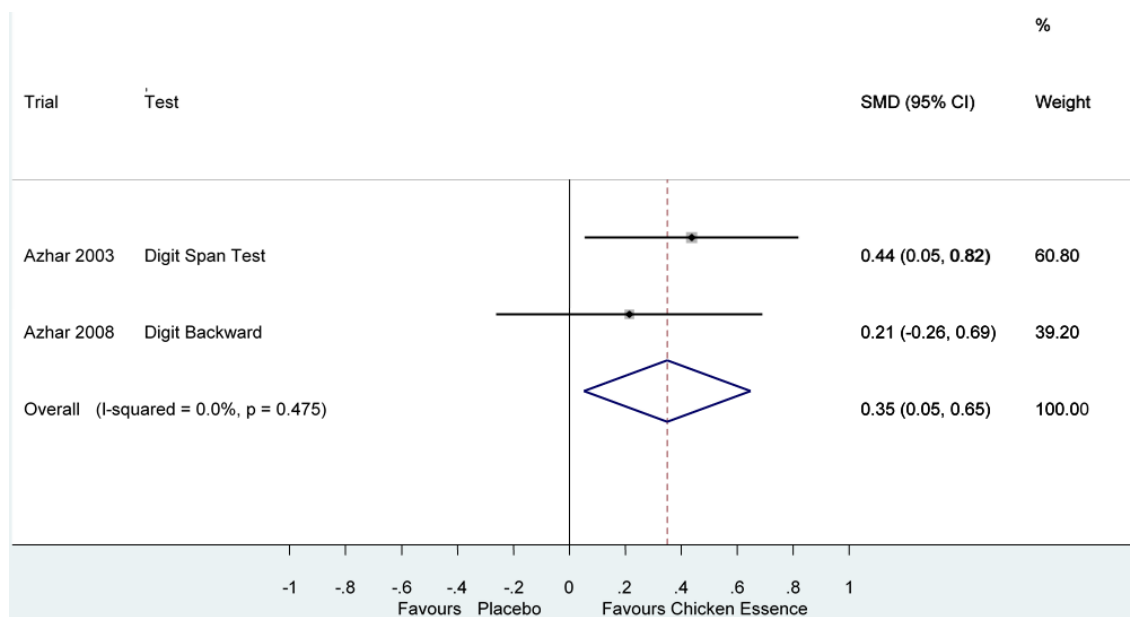


Figure D1. Pooled effect estimate of score of longest list of digits remembered of executive function tests (with Azhar's test removed [2]).

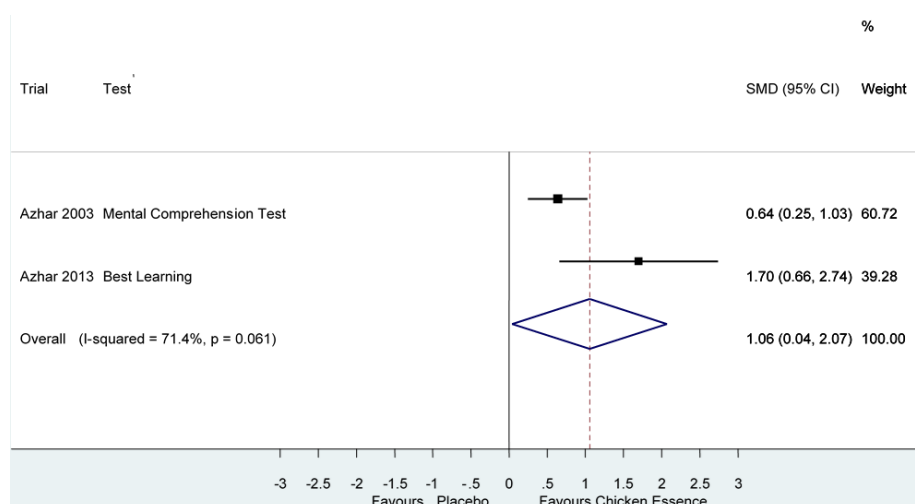


Figure D2. Pooled effect estimate of score of short-term memory tests (with Azhar's test removed [15]).

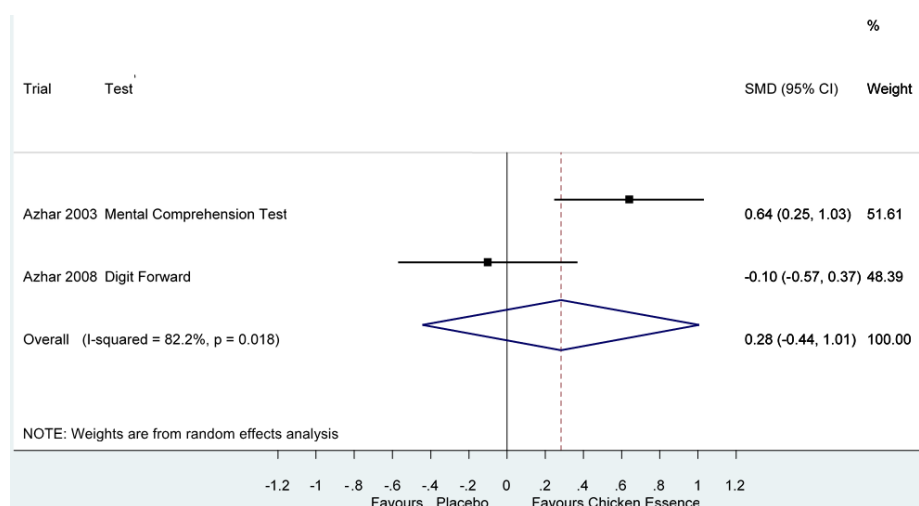


Figure D3. Pooled effect estimate of score of short-term memory tests (with Azhar's test removed [2]).

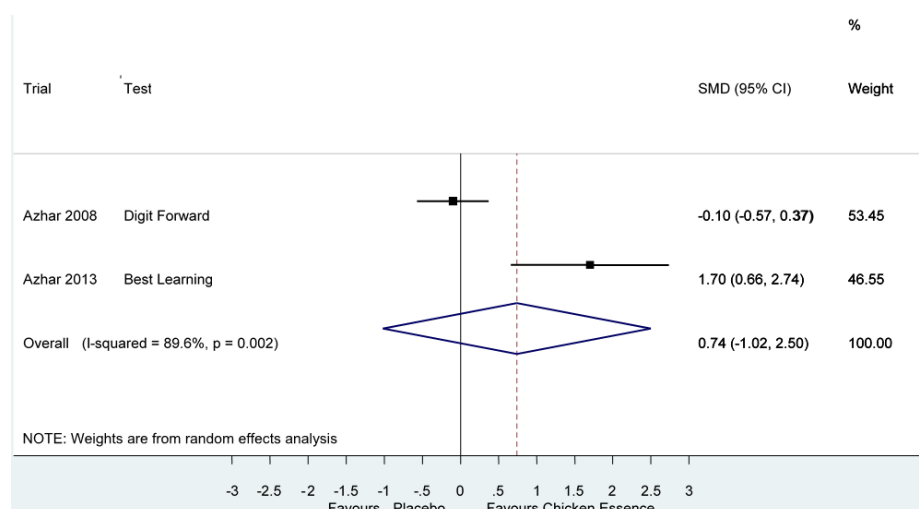


Figure D4. Pooled effect estimate of score of short-term memory tests (with Azhar's test removed [14]).

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STUDY PROTOCOL

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Room temperature stable carbetocin for the prevention of postpartum haemorrhage during the third stage of labour in women delivering vaginally: study protocol for a randomized controlled trial

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Abstract

Background: Postpartum haemorrhage (PPH) is the leading cause of maternal mortality in low-income countries and contributes to nearly a quarter of maternal deaths globally. The current available interventions for prevention of postpartum haemorrhage, oxytocin and carbetocin, are limited by their need for refrigeration to maintain potency, as the ability to maintain a cold chain across the drug distribution and storage network is inconsistent, thus restricting their use in countries with the highest burden of maternal mortality. We describe a randomized, double-blind non-inferiority trial comparing a newly developed room temperature stable formulation of carbetocin to the standard intervention (oxytocin) for the prevention of PPH after vaginal birth.

Methods/design: Approximately 30,000 women delivering vaginally will be recruited across 22 centres in 10 countries. The primary objectives are to evaluate the non-inferiority of room temperature stable carbetocin (100 µg intramuscular) versus oxytocin (10 IU intramuscular) in the prevention of PPH and severe PPH after vaginal birth. The primary endpoints are blood loss ≥ 500 mL or the use of additional uterotonics (composite endpoint required by drug regulatory authorities) and blood loss $\geq 1,000$ mL (WHO requirement). Non-inferiority will be assessed using a two-sided 95 % confidence interval for the relative risk of the above endpoints for room temperature stable carbetocin versus oxytocin. The upper limit of the two-sided 95 % confidence interval for the relative risk for the composite endpoint of blood loss ≥ 500 mL or the use of additional uterotonics, and for the endpoint of blood loss $\geq 1,000$ mL, will be compared to a non-inferiority margin of 1.16 and 1.23, respectively. If the upper limit is below the corresponding margin, non-inferiority will have been demonstrated. The safety analysis will include all women receiving treatment. Safety and tolerability will be assessed by a review of adverse events, by conducting inferential testing with significance levels for between-group comparisons.

(Continued on next page)

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(Continued from previous page)

Discussion: If the results of the study show that room temperature stable carbetocin is a safe and effective alternative to oxytocin, this could have a substantial impact on the prevention of postpartum haemorrhage and maternal survival worldwide.

Trial registration: ACTRN12614000870651 (14 August 2014)

Keywords: Postpartum haemorrhage, Room temperature stable carbetocin, Oxytocin, Non-inferiority trial

Background

Postpartum haemorrhage (PPH) is defined as a blood loss of ≥ 500 mL within 24 hours of delivery, while severe PPH (sPPH) is defined as a blood loss of $\geq 1,000$ mL within the same time frame [1]. PPH is the leading cause of maternal mortality in low-income countries, contributing to nearly a quarter of maternal deaths globally. In addition, PPH is a significant contributor to severe maternal morbidity and long-term disability, as well as to a number of other severe maternal conditions generally associated with more substantial blood loss, including shock and organ dysfunction [2–4]. Improving health care for women during childbirth in order to prevent and treat PPH is an essential step towards the achievement of the United Nations Millennium Development Goals.

The majority of deaths due to PPH could be avoided through the use of prophylactic uterotonics during the third stage of labour and by timely and appropriate management. Injectable oxytocin has been recommended by the World Health Organization (WHO) for routine use during the third stage of labour and is the preferred drug for the prevention and management of blood loss after childbirth; however, several studies have demonstrated that oxytocin loses potency in field conditions, particularly in tropical climates [1, 5, 6]. To decrease potency loss due to degradation, oxytocin must be either stored at controlled room temperature (25 °C or lower) for a restricted amount of time or refrigerated (2 °C to 8 °C), making its use difficult in low resource settings. To ease this barrier, several groups have been researching heat stable oxytocin formulations [5]. Though some progress has been made in this area, there is currently no heat stable oxytocin formulation for therapeutic use [7].

Carbetocin (1-deamino-1-monocarba-(2-O-methyl-tyrosine)-oxytocin) is a long-acting synthetic agonist analogue of the human oxytocin, and it appears to be a promising agent in the prevention of PPH following vaginal delivery. The clinical and pharmacological properties of carbetocin are similar to those of oxytocin. However, carbetocin is a more stable molecule and induces a prolonged uterine response, when administered postpartum, in terms of both amplitude and frequency of contractions due to its longer half-life [8–10]. In a Cochrane systematic review including 11 studies (2,635 women), the use of

carbetocin resulted in a statistically significant reduction in the use of additional/therapeutic uterotonics compared to oxytocin for those who underwent caesarean delivery (risk ratio (RR) 0.62; 95 % confidence interval (CI) 0.44 to 0.88; four trials, 1,173 women), but not for vaginal delivery. Compared to oxytocin, carbetocin was associated with reduced uterine massage following both caesarean delivery (RR 0.54; 95 % CI 0.37 to 0.79; two trials, 739 women) and vaginal delivery (RR 0.70; 95 % CI 0.51 to 0.94; one trial, 160 women). There were no statistically significant differences between carbetocin and oxytocin in terms of risk of any PPH or in risk of sPPH [11].

Carbetocin is currently approved in multiple countries for the prevention of PPH during caesarean section. The drug is licensed to be administered by slow intravenous (IV) single injection at a dose of 100 µg. Its current formulation requires refrigeration.

A room temperature stable (RTS) variant of carbetocin has recently been developed and is now approved in the European Union; this variant differs from the current carbetocin formulation only in its excipients (Table 1). The stability data from long-term studies performed at 30 °C and 75 % relative humidity, as well as accelerated at 40 °C and 75 % relative humidity, indicate a shelf life of at least 36 months at 30 °C for the new RTS formulation of carbetocin. Carbetocin RTS therefore represents a promising intervention for reducing PPH, particularly in settings where cold storage is difficult to achieve and maintain. Here, we describe a planned randomized trial to evaluate the non-inferiority of carbetocin RTS versus oxytocin after vaginal delivery in the prevention of PPH and sPPH.

Methods/design

Primary objectives and hypotheses

The trial has two primary objectives: 1) To evaluate non-inferiority of carbetocin RTS versus oxytocin after vaginal delivery in the prevention of the composite endpoint “blood loss of 500 mL or more or the use of additional uterotonics” at one hour and up to two hours for women who continue to bleed after one hour; and 2) to evaluate non-inferiority of carbetocin RTS versus oxytocin in the prevention of sPPH ($\geq 1,000$ mL blood loss) at one hour and up to two hours for women who continue to bleed after one hour.

Table 1 Composition of carbetocin RTS and carbetocin

New carbetocin RTS formulation			Current carbetocin refrigerated formulation (Duratocin®, Ferring) ^a		
Component	Amount (mg/mL)	Function	Component	Amount (mg/mL)	Function
Carbetocin	0.100	Active substance	Carbetocin	0.100	Active substance
Succinic acid	1.19	Buffer	Sodium chloride	9	Isotonicity agent
Mannitol	47.0	Isotonicity agent	Glacial acetic acid	to pH 3.8	pH adjustment
L-methionine	1.00	Antioxidant	Water for injection	1.0 mL	Solvent
Sodium hydroxide 2 N	to pH 5.45	pH adjustment	–	–	–
Water for injection	1.0 mL	Solvent	–	–	–

^aCarbetocin 100 µg/mL was first approved in Canada in June 1997 and is currently registered in more than 70 countries under the trade names PABAL/DURATOCIN/LONACTENE/DURATOBAL
RTS room temperature stable

For both objectives the hypotheses are: 1) carbetocin RTS is non-inferior to oxytocin in terms of the proportion of women with blood loss ≥ 500 mL or the use of additional uterotonic drugs after vaginal delivery within a non-inferiority margin of 1.16 on the relative risk scale, and the proportion of women with blood loss $\geq 1,000$ mL after vaginal delivery within a non-inferiority margin of 1.23 on the relative risk scale; and 2) carbetocin RTS is superior to oxytocin in terms of the proportion of women with blood loss ≥ 500 mL or use of additional uterotonic drugs, and in terms of the proportion of women with blood loss $\geq 1,000$ mL after vaginal delivery. For each of the two primary endpoints, superiority will be tested if non-inferiority has been demonstrated.

Investigators and other assessors will be blinded to individual treatment allocation. The study will be conducted by the HRP/WHO, and WHO staff will also remain blinded to individual participant treatment allocation during the conduct of the trial.

Study drug

Carbetocin RTS (Ferring, St. Prex, Switzerland) will be administered as a single IM dose of 100 µg in a 1 mL solution. Oxytocin 10 IU/mL (Syntocinon®, Novartis, Basel, Switzerland) will be administered as a single intramuscular (IM) dose in a 1 mL solution. In order to maintain the blindness of the trial, carbetocin RTS and oxytocin will be provided in 1 mL ampoules in consecutively numbered treatment packs arranged in dispensers and will be stored in a refrigerator at 2 °C to 8 °C.

Study design

This clinical trial will be conducted in compliance with the clinical trial protocol, good clinical practice and the applicable regulatory requirements. The trial is planned to be conducted at 22 centres in 10 countries: Argentina, Egypt, India, Kenya, Nigeria, Singapore, South Africa, Thailand, Uganda and the United Kingdom. Approximately 30,000 women will be included in the trial. The recruitment period will be approximately 12 months in each country.

The care provider in charge of antenatal care visits at the hospital will inform potentially eligible pregnant women (women with no allergies to carbetocin, other oxytocin homologues or excipients, or serious cardiovascular disorders) about the trial.

At admission for labour at the hospital, the woman will be approached for participation in the trial when she is in early labour and if her vital signs are normal, and she is not stressed. The investigator will invite her to sign the informed consent. Informed consent will be obtained before any trial-related procedures are carried out.

During the second stage of labour when vaginal delivery is imminent, the woman will be randomized to receive either a single dose of oxytocin 10 IU IM or a single dose of carbetocin RTS 100 µg IM.

The investigator will administer the investigational medicinal product (IMP) immediately after the birth of the baby (preferably within one minute). Once the IMP has been administered, the investigator will follow the management of the third stage of labour as recommended in WHO guidelines and as detailed in the trial's manual of operations.

Once the cord is clamped (1–3 minutes after delivery of the baby) and cut, the investigator will place a calibrated drape under the woman's buttocks and blood loss will be measured for one hour or two hours postpartum if the bleeding continues beyond one hour (blood loss measuring details are provided in the trial's manual of operations).

The woman will end her participation in the trial after her discharge or if she is transferred to a higher care unit, such as an intensive care unit (ICU). Data will be entered into a validated online database system compliant with the FDA 21 CFR part 11.

The trial master protocol was approved by the World Health Organization Research Ethics Review Committee. All sites received ethics approval from their institutional/national boards (see additional file 1 for the list of ethics committees that reviewed and approved the proposal).

Inclusion/exclusion criteria

Women will be eligible for inclusion into this trial if they are expected to deliver vaginally, have a cervical dilatation equal to or less than 6 cm, have a known singleton pregnancy and have provided written informed consent. Women will not be eligible for study participation if they: 1) are in an advanced first stage of labour (>6 cm cervical dilatation) or are too distressed to understand, confirm and give informed consent regardless of cervical dilatation; 2) are non-emancipated minors (as per local regulations) without a guardian; 3) have been scheduled for a planned caesarean section; 4) have a birth considered to be an abortion according to local guidelines; 5) have known allergies to carbetocin, other oxytocin homologues or excipients in the medicinal products used in the trial; 6) have serious cardiovascular disorders; 7) have serious hepatic or renal disease; 8) have epilepsy; or 9) are not capable of giving consent due to other health problems such as obstetric emergencies (for example, antepartum haemorrhage) or mental disorder.

Participants will be free to discontinue the trial at any time without giving their reason(s). Participants who withdraw will not be replaced; that is, randomized numbers will be uniquely linked to each participant. Data collected up to that point will be included unless participants request the opposite. After a participant has completed the trial or has withdrawn early, usual treatment will be administered, if required, in accordance with the trial centre's standard of care and generally accepted medical practice and depending on the participant's individual medical needs.

Randomization

The random allocation sequence will be generated centrally at WHO headquarters using computer-generated random numbers. Randomization will be stratified by country and will use permuted blocks, with an allocation ratio of 1:1. Participants will randomly be assigned within each country to one of the two treatment groups: oxytocin 10 IU IM or carbetocin RTS 100 µg IM. Allocation of the randomly generated sequence will be performed by consecutively numbered treatment packs arranged in dispensers.

Primary and secondary endpoints

The primary and secondary endpoints are listed in Table 2. The trial is being conducted as an effectiveness trial with the objective of carbetocin RTS being registered for the indication "prevention of postpartum haemorrhage" by drug regulatory authorities if it is shown to be non-inferior or superior to oxytocin. The primary composite endpoint is blood loss ≥ 500 mL or use of additional uterotonics. For the purpose of evaluating clinical effectiveness and for the potential inclusion

Table 2 Primary and secondary endpoints

Primary endpoints

The proportion of women:

- with blood loss of 500 mL or more or the use of additional uterotonics at one hour and up to two hours for women who continue to bleed after one hour;
- with blood loss of 1,000 mL or more at one hour and up to two hours for women who continue to bleed after one hour.

Secondary endpoints

The proportion of women:

- with blood loss of 500 mL or more at one hour (or two hours postpartum if the bleeding continues beyond one hour);
 - receiving additional uterotonics at one hour (or two hours postpartum if the bleeding continues beyond one hour);
 - receiving additional uterotonics up to time of discharge;
 - receiving blood transfusion up to time of discharge;
 - with manual removal of placenta up to time of discharge;
 - having additional surgical procedures (for example, suturing of cervix/high vaginal tear, exploration of uterine cavity under general anaesthetic, uterine compression suture, uterine or hypogastric ligation, hysterectomy) up to time of discharge;
 - with maternal death;
 - with composite outcome of maternal death or severe morbidity (admission to intensive care unit, hysterectomy, blood loss of two litres or more, uterine inversion) up to time of discharge.
- Blood loss in mL at one hour (or two hours postpartum if the bleeding continues beyond one hour).
The incidence and severity of adverse or serious adverse events up to the time of discharge.
Newborn outcomes (vital status, Apgar score at 5 minutes, resuscitation of the baby, mechanical ventilation).

of carbetocin RTS in future WHO guidelines and the Model List of Essential Medicines, the more substantive endpoint of blood loss $\geq 1,000$ mL is also a primary endpoint. Since the two primary endpoints serve independent objectives, there will be no adjustment for the type I error rate for multiplicity of endpoints.

Assessment of efficacy

Efficacy will be assessed using blood loss volume measurement per the two primary endpoints listed in Table 2. Blood loss will be measured using a calibrated drape [12], which will be placed under the participant's buttocks once the cord is clamped (1–3 minutes after delivery of the baby) and cut. Blood loss will be measured for one hour, or for two hours postpartum, if the bleeding continues beyond one hour. Blood loss weight in grams will be converted to millilitres by dividing the figure in grams by 1.06 (blood density in grams per millilitre) [13].

Assessment of safety

Comprehensive assessment of the safety of the study drugs will be performed throughout the course of the trial, from the time of the participant's signature of informed consent until discharge. Trial centre personnel will report any adverse event (AE), whether observed by the investigator or reported by the participant.

The intensity of an AE will be classified using a three-point scale: mild — awareness of signs or symptoms, but no disruption of usual activity; moderate — event sufficient to affect usual activity; and severe — inability to work or perform usual activities. AEs will also be classified as possibly related to study drug (that is, there is evidence or argument to suggest a causal relationship between the AE and the study drug), or not related to study drug (that is, there is no reasonable evidence or argument to suggest a causal relationship between the AE and the study drug).

The outcome of an AE will be classified as: recovered/resolved (fully recovered or the condition has returned to the level observed at initiation of trial treatment); recovered/resolved with sequelae (resulted in persistent or significant disability/incapacity); recovering/resolving; not recovered/not resolved; or fatal.

An AE will be considered serious if it results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is an important medical event. If an investigator becomes aware of a serious AE after the participant's hospital discharge, and he/she assesses the serious AE to have a reasonable possible causality to the study drug, the case will be reported, regardless of how long after the end of the trial the AE took place.

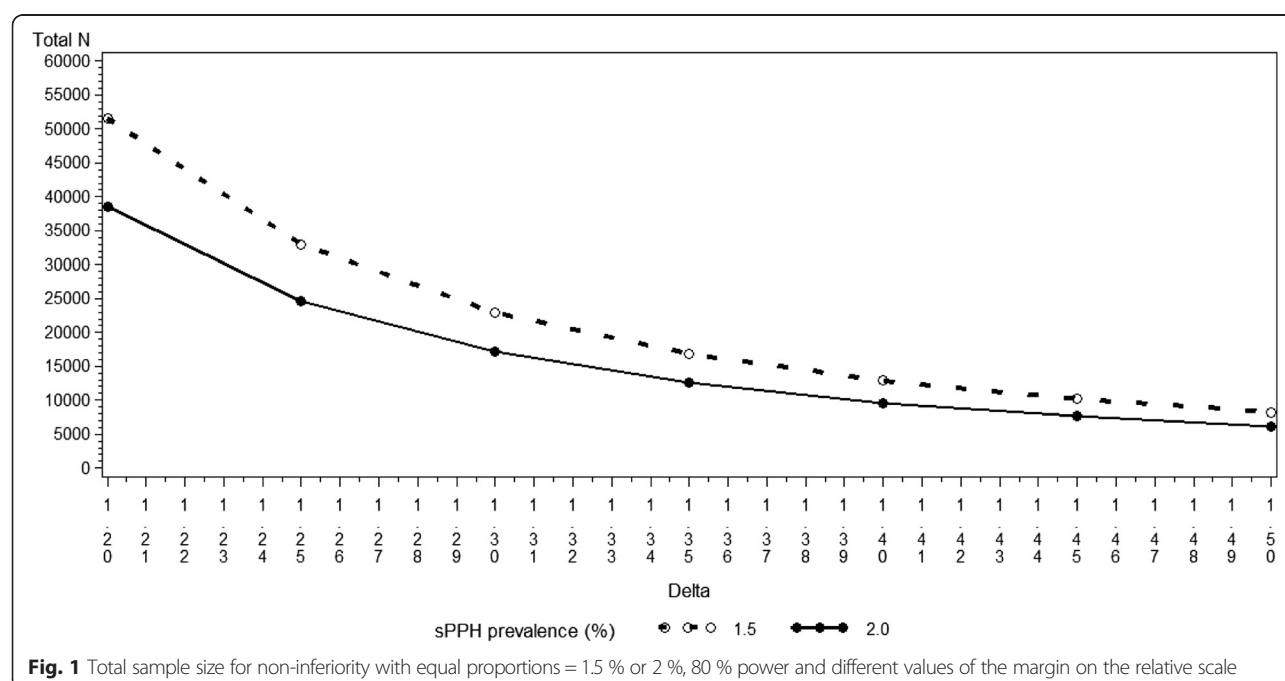
Since the amount of blood lost is collected as an efficacy endpoint, only the following blood loss events that fulfil the criteria for a serious AE will be recorded: ICU admission (adult ICU admission, not maternity/labour

ward high care); surgical intervention for control of haemorrhage (hypogastric artery ligation or uterine compression sutures); peripartum hysterectomy, blood loss $\geq 2,000$ mL; and uterine inversion.

Sample size calculation

The two endpoints that guided the sample size estimation for the trial were sPPH (blood loss $\geq 1,000$ mL), PPH (blood loss ≥ 500 mL) or the use of additional uterotonics. Severe PPH is a more serious endpoint that is closely associated to severe maternal morbidity and related to additional interventions. The sPPH endpoint is also less frequent and thus guided the overall sample size estimation.

A non-inferiority design was chosen since the aim of the trial is to determine if carbetocin RTS is non-inferior in efficacy to the standard intervention (oxytocin 10 IU IM). In order to demonstrate non-inferiority within a margin of 0.46 %, with a power of 80 % and with a significance level of 2.5 %, a total of 29,082 women are needed assuming an equal sPPH prevalence of 2 % with both treatments, calculated by the standard formula (see Additional file 2 for the rationale of the choice of the margin) [14]. The margin of 0.46 % on the difference scale corresponds to 1.23 on the relative scale for the assumed prevalence. Figure 1 shows the total sample size required to assess non-inferiority at the 2.5 % level of significance (usually required for non-inferiority trials) for different scenarios. We also assumed, from a similar large trial [15], a 3 % loss of study participants who are eligible to contribute to the analysis due to exclusion of women



with a caesarean section or abortion after randomization, and those who are not protocol-compliant (excluded only in the per-protocol analysis), bringing the sample size to 30,000. This sample size will provide 90 % power for a conventional two-sided 5 % test of superiority to detect a minimum significant difference between 1.5 % and 2 % in the rate of sPPH for the two treatment groups.

Similarly, we calculated the sample size for the composite endpoint defined as blood loss ≥ 500 mL or administration of additional uterotonics. With active management, the risk of this event is estimated as 16 % (personal communication) [15]. Assuming equal prevalence for this event of 16 % with both treatments, in order to demonstrate non-inferiority within a margin of 1.16 on the relative scale, with a power of 80 % and with a significance level of 2.5 %, a total of 6,242 women are needed. With 30,000 women the power obtained would be more than 99 % [14]. This sample size will provide a power of 99.5 % for a conventional two-sided 5 % test of superiority to detect a minimum significant difference between 16 % and 18 % in the occurrence of PPH or administration of additional uterotonics for the two treatment groups (Stata version 13.1).

Analysis populations

Analyses will be performed in three populations: intention-to-treat (ITT), modified ITT, and per-protocol. The ITT population includes all randomized participants, using the treatment as randomized. The modified ITT analysis excludes women having a caesarean section after randomization and those withdrawing consent. The per-protocol population includes all participants randomized into the trial, who were compliant with, and treated according to, the protocol, and who fulfil the following criteria: compliance with all entry criteria, absence of major clinical trial protocol violations with respect to factors likely to affect the efficacy of treatment, and adequate compliance with trial medication (giving oxytocin or carbetocin to women as randomized). Declaring carbetocin RTS non-inferior to oxytocin will require non-inferiority to be demonstrated for both per-protocol and the modified ITT analyses. For testing the superiority of each endpoint, the modified ITT analysis will be the main analysis. The primary population for safety analysis will consist of all women receiving treatment.

Statistics

Safety and tolerability will be assessed by a review of AEs, by conducting inferential testing with significance levels for between-group comparisons. The between-treatment difference for the occurrence of AEs will be tested using the stratified Mantel-Haenszel chi-square if

frequencies are sufficiently high, or otherwise with exact methods taking stratification into account.

For efficacy, non-inferiority will be assessed using a two-sided 95 % confidence interval (CI) for the relative risk (RR) of sPPH and of PPH or additional uterotonic use (carbetocin RTS versus oxytocin). The upper limit of the two-sided 95 % CI for the RR for the composite endpoint of blood loss ≥ 500 mL or additional uterotonic use will be compared to the non-inferiority margin of 1.16. The upper limit of the two-sided 95 % CI for the RR for the endpoint of blood loss $\geq 1,000$ mL will be compared to the non-inferiority margin of 1.23. If the upper limit is below the corresponding margin, non-inferiority will have been demonstrated. This upper limit is the same as the upper limit of the one-sided 97.5 % CI; therefore, the significance level for the non-inferiority test will be 2.5 % (one-sided). For each endpoint, to declare carbetocin RTS non-inferior to oxytocin, we will require non-inferiority to be demonstrated for both PP and the modified ITT analyses. If non-inferiority is demonstrated, a two-tailed superiority test will be conducted at 5 % level of significance. Interpretation will be as in Fig. 1 of Piaggio et al. [16]. Comparisons will also be expressed as risk differences with 95 % CIs.

The statistical technique used to conduct tests and obtain CIs for the main endpoints will be a logistic model with a binary endpoint, a binomial distribution and the log link to obtain RRs. The identity link will be used to obtain risk differences. Stratifying variables (country) will be included in the model. The model will be fitted using SAS Software version 9.3 (SAS Institute Inc., Cary, NC, USA). A separate model will be fitted for each of the two primary endpoints.

We will use the RR as measure of treatment effect on the relative scale for the two primary endpoints. For the composite endpoint of blood loss ≥ 500 mL or use of additional uterotonics, the margin has been justified as 1.2 on the odds ratio (OR) scale and 1.16 on the RR scale. Heterogeneity across centres will be assessed by using a term in the logistic model for the interaction between treatment and centres. If there is heterogeneity between the centres for any of the results, the possible causes will be explored.

The secondary binary endpoints of blood loss ≥ 500 mL, use of additional uterotonics, blood transfusion, manual removal of placenta, additional surgical procedures, maternal death and the composite endpoint of maternal death or severe morbidity, will be analysed using the modified ITT population and will be assessed only for conventional superiority using risk differences and relative risks with 95 % CIs estimated with the same techniques described for the main endpoints.

The secondary outcome of blood loss in millilitres will be analysed using the log transformation. This is based on the following: 1) the blood loss distribution is

positively skewed; 2) different distributions were fitted to blood loss data from a large trial [15] and the lognormal distribution was found to have a very good fit (personal communication); and 3) the lognormal distribution was used for blood loss data in the literature [13]. Therefore, a lognormal distribution will be fitted to the blood loss data and the probabilities of blood loss ≥ 500 mL and of $\geq 1,000$ mL will be compared between treatments using parametric methods. The quantiles will be compared between treatments using quantile regression [17].

Trial oversight

The trial will be overseen by two committees. The Trial Steering Committee (TSC) is composed of the WHO/HRP coordination team, investigators from the 10 participating countries and five independent members with expertise in clinical, statistical and scientific disciplines. The TSC should provide oversight of the progress of the trial and ensure the trial is conducted in accordance with the principles of good clinical practice (GCP).

The Data and Safety Monitoring Committee (DSMC), with no direct involvement in the trial, will handle any ethical issues that may arise while the trial is in progress and will scrutinize two interim analyses, the first to look at safety when 5,000 participants have been recruited, and the second conducted when 15,000 women have been recruited to look at both safety and efficacy. The interim analyses will be masked to trial investigators, trial statistician, WHO, Merck for Mothers and Ferring staff, but not to DSMC members. The DSMC will be expected to provide an ongoing risk-benefit evaluation that addresses the uncertainty necessary to continue.

Discussion

PPH is one of the major contributors to maternal mortality and morbidity worldwide. Prevention of PPH is therefore of great importance in the pursuit of improved health care for women. The decision to proceed with a large, randomized controlled trial to address this unmet medical need by evaluating the effectiveness of carbetocin RTS compared to oxytocin was based on several considerations. This included the frequent concerns about the quality of oxytocin and its stability in some developing countries, the potential advantage of carbetocin RTS due to its longer half-life (than that of oxytocin), especially when administered intramuscularly, and its heat stability. This study will be conducted under conditions where both study drugs, oxytocin and carbetocin RTS, will be kept under strict refrigeration. If the trial meets its primary endpoint of non-inferiority to oxytocin, the carbetocin RTS formulation will be made available in high-burden countries at an accessible public sector price. This would have major implications for

expanding access to effective care and could have a substantial impact on maternal survival.

The risk-benefit relationship was carefully considered in the planning of the trial, as was the selection of the dose of carbetocin RTS. The selected dose for the carbetocin RTS IM injection is 100 μ g, the same as the dose approved for IV injection following caesarean section. The safety profile of a 100 μ g dose of the carbetocin refrigerated formulation, when administered intravenously, is derived from clinical studies as well as from pharmacovigilance activities that comprise nearly 5 million women exposed. Reported AEs during clinical trials when administered by IV after caesarean section under spinal or epidural anaesthesia are headache, tremor, hypotension, flushing, nausea, abdominal pain, pruritus, anaemia, dizziness, chest pain, dyspnoea, metallic taste and vomiting. The AEs observed were of the same type and frequency as those observed with the comparator, oxytocin. In addition, efficacy and safety data on 100 μ g of the carbetocin refrigerated formulation delivered intramuscularly during vaginal delivery is available from several published randomized clinical trials [11, 18, 19]. Although the population from whom these safety data are generated is different from the study population of this protocol, women undergoing caesarean section are expected to be at the same or higher risk of AEs than women having a vaginal delivery. It is therefore expected that a carbetocin RTS dose of 100 μ g IM, when used in women after vaginal delivery, will be efficacious and have a safety profile that is equal to or better than the well-characterized safety profile of 100 μ g IV when used in women following caesarean section.

The study has several strengths. It is a global, multi-centred, randomized, double-blind, active comparator controlled study. The active comparator is oxytocin, which is the most commonly recommended drug for PPH prophylaxis and considered the current gold standard in WHO guidelines. The 10 IU dose of oxytocin was chosen as this is currently the most commonly used dose in clinical practice internationally when IM administration is practiced. Blood loss of $\geq 1,000$ mL is a primary endpoint in this trial, as it was considered as one of the three critical endpoints (together with blood transfusion and maternal death) for the earlier 2007 WHO recommendations for PPH prevention where outcomes were rated by an independent panel [1]. We also used reliable estimates of prevalence of blood loss $\geq 1,000$ mL under active management with oxytocin from different trials and systematic reviews. Additionally, an external DSMC has been established for the ongoing assessment of the risk-benefit ratio. One limitation of our study is that the predicted sample size makes assumptions that in reality might not hold. For example, if the efficacy of oxytocin is much better than that of carbetocin RTS, this would imply that non-inferiority is not likely to be demonstrated and the trial should be stopped for futility. If

oxytocin is just slightly better than carbetocin RTS, the predicted sample size could have been underestimated, but this is not likely given previous evidence [11].

Results of this trial will be extremely useful, particularly in tropical settings, where cold storage is difficult to achieve and maintain. Should this trial demonstrate that carbetocin RTS is non-inferior to oxytocin in preventing postpartum haemorrhage, in settings where the cold chain cannot be guaranteed, oxytocin could be replaced by carbetocin RTS as the uterotonic used during the third stage of labour. In addition, and based on the tripartite agreement signed between WHO/HRP, Merck for Mothers and Ferring Pharmaceuticals, carbetocin RTS could be available in high-burden countries at a public sector price comparable to oxytocin's price. This could have major implications for preventing PPH and a substantial impact on maternal survival worldwide.

Trial status

The trial has started recruitment in five countries. The other five countries are expected to receive regulatory authorities' approval before April 2016.

Additional files

Additional file 1: Countries ethics committees list and status of the project approval request. (DOCX 15 kb)

Additional file 2: Rationale for the choice of the non-inferiority trial the choice of the non-inferiority trial [20-22]. (DOCX 24 kb)

Abbreviations

AE: adverse event; CI: confidence interval; DSMC: Data Safety Monitoring Committee; GCP: good clinical practice; HRP: the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction; IM: intramuscular; IMP: investigational medicinal product; ITT: intention to treat; IU: international unit; IV: intravenous; mL: millilitres; PPH: postpartum haemorrhage; RHR: reproductive health and research; RR: risk ratio; RTS: room temperature stable; SAE: serious adverse event; sPPH: severe postpartum haemorrhage; TSC: Trial Steering Committee; WHO: World Health Organization.

Competing interests

The authors declare that they have no competing interests. WHO/HRP is solely responsible for the trial. Merck for Mothers is providing the funding and Ferring Pharmaceuticals the carbetocin RTS. The collaboration between WHO/HRP, Merck for Mothers and Ferring Pharmaceuticals is governed by a tripartite agreement.

Authors' contributions

The protocol was written by AMG, GP and MW (WHO/HRP coordination team) with comments and contributions from HA, GC, YSC, AC, BF, SG, GJH, PL, KM, TMHN, ZQ and JPS (country investigators and members of the Trial Steering Committee). All authors contributed to the development of the trial protocol and approved the submitted manuscript.

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Reply

Reply to C. Stewart's Letter to the Editor Re: Teoh SL *et al.*, *Nutrients* 2016, 8, 57

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In a recent systematic review and meta-analysis report (*Nutrients* 2016, 8, 57), we critically appraised and summarized current evidence to determine the effects of chicken essence in improving cognitive functions as well as its safety. Our report showed a lack of convincing evidence to support the cognitive-enhancing effects of chicken essence. A critique of our work appeared in *Nutrients* (Stewart C Letter to the Editor 2016, 8, 201). In this Reply, we have endeavored to respond to each point highlighted by Stewart, commencing with corrections to our original report.

1. Corrections

Stewart identified an error in our report—"Table 4 identifies Executive Function, WAIS arithmetic test, Azhar 2008 as significant, but the 95% CI includes zero". We thank Stewart for identifying this error and wish to make the following corrections.

1.1. In Table 4, Executive Function Domain

The star denoting a significant difference in the WAIS-Arithmetic test in Azhar 2008 should be removed.

1.2. In Section 3.4. Effects of Chicken Essence in Cognitive Function Improvement—First Paragraph

"Of the 30 complete data, 12 (instead of 13) were found to have significant differences between CE group and placebo group, where seven (instead of eight) were in executive function domain, and five in short-term memory domain".

2. Small Number of Studies Included

Stewart questions the exclusion of a large number of studies when the grounds for inclusion were very broad. The inclusion criteria were carefully defined using the PICO framework to be specific to our research question [1]. However, we acknowledge that the number of excluded studies at the screening stage is large. This is because we did not initially limit our search strategy to human randomized controlled trials (RCTs) and we searched using subject terms only [2].

3. Underpowered Clinical Trials and High Drop-Out Rates

Stewart asserts that including trials with small number of subjects and high drop-out rates provides unwarranted results. We agree that the number of subjects recruited in individual trials was relatively small. Therefore, the need to perform a meta-analysis is warranted as the power would be increased by combining multiple studies. We acknowledge that a high drop-out rate in a trial can cause attrition bias, which was fully assessed in “incomplete outcome reporting” domain of Cochrane’s risk of bias tool. Therefore, we would argue that we have presented the pooled findings with explicit consideration of its implication on our confidence in interpreting the findings instead of presenting unwarranted results.

4. Heterogeneity of Trials

4.1. Subject Characteristics and Chicken Essence Regimens

Stewart refutes combining cognitively impaired subjects with healthy subjects and combining trials with heterogeneous regimens of chicken essence (CE). In addition, he asserts that healthy subjects of young age were less likely to show a cognitive effect even if one existed. We acknowledged that the trials combined in our primary analysis had the heterogeneity issue. Therefore, we conducted further analysis to remove the heterogeneity by excluding the trial with subjects of poorer cognitive function and different CE regimen. The further analysis, which combined trials with healthy subjects of young age and similar CE regimens only, showed a pooled result with a significant difference and another pooled result with no significant difference [3].

4.2. Cognitive Function Tests and RCT Designs

Stewart refutes combining trials with different cognitive function tests. We acknowledge the differences in the cognitive function tests. Therefore, we pooled data only from the most comparable cognitive function tests and used standardized mean difference (SMD) to address the differences in measurement scales [4].

Stewart refutes combining trials with different designs. However, combining data from a parallel trial (The parallel trial in Table 5 of [3] should be Young 2015 (instead of Yamano 2015)) and a cross-over trial has been widely accepted [5].

5. Chicken Meat Ingredient-168 (CMI-168)

Stewart refutes the inclusion of the trial which used CMI-168 in the intervention group. However, CMI-168 was still considered as CE based on its description of “a hydrolyzed chicken extract prepared from chicken meat that had been processed by a proprietary technology” [6]. This definition was consistent with the definition of CE used in our report. Therefore, we remain assured that the trial was appropriate for inclusion.

6. Poor Quality of Trials

Stewart asserts that synthesizing evidence from poor quality trials provides unreliable results. We agree that the poor quality of trials reduced the confidence in the effect estimate and this was highlighted using the GRADE approach in our report. Therefore, we stressed in the report the necessity of interpreting the findings of the meta-analysis with caution.

7. Comparison with the Effect of Carnosine

Stewart refutes our decision to relate the effect of CE with the effect of carnosine. We agree that carnosine might not be exactly the same as CE. However, carnosine is documented as one of the primary active contents of CE [7–9]. We chose carnosine for comparison because it was the closest

product to CE. The readers would benefit from seeing how our CE findings would be compared to a similar product.

8. Conclusions

In conclusion, we show in this reply that the issues raised by Stewart were not ignored but highlighted with sound methods. Our report is useful as an exploratory meta-analysis [10] to provide a plausible effect estimate and to identify gaps in the RCTs in evaluating the cognitive effects of CE.

We are grateful to Stewart for bringing our attention to some pertinent issues in the conduct of systematic review and meta-analysis, and for giving us an opportunity to reassess our work from his perspective.

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Conflicts of Interest: The authors declare no conflict of interest.

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STUDY PROTOCOL

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Global, regional and national levels and trends of preterm birth rates for 1990 to 2014: protocol for development of World Health Organization estimates

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Abstract

Background: The official WHO estimates of preterm birth are an essential global resource for assessing the burden of preterm birth and developing public health programmes and policies. This protocol describes the methods that will be used to identify, critically appraise and analyse all eligible preterm birth data, in order to develop global, regional and national level estimates of levels and trends in preterm birth rates for the period 1990 – 2014.

Methods: We will conduct a systematic review of civil registration and vital statistics (CRVS) data on preterm birth for all WHO Member States, via national Ministries of Health and Statistics Offices. For Member States with absent, limited or lower-quality CRVS data, a systematic review of surveys and/or research studies will be conducted. Modelling will be used to develop country, regional and global rates for 2014, with time trends for Member States where sufficient data are available. Member States will be invited to review the methodology and provide additional eligible data via a country consultation before final estimates are developed and disseminated.

Discussion: This research will be used to generate estimates on the burden of preterm birth globally for 1990 to 2014. We invite feedback on the methodology described, and call on the public health community to submit pertinent data for consideration.

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Background

Background, rationale, aims and objectives

Preterm birth (PTB) is defined by WHO as all births before 37 completed weeks of gestation [1]. Preterm neonates are at an increased risk for a wide range of short- and long-term respiratory, infectious, metabolic and neurological morbidities, with higher risks of adverse outcomes seen at

lower gestational ages [2, 3]. Of the estimated 6.3 million children under 5 who died in 2013, 15.4 % (0.965 million, uncertainty range 0.615–1.537 million) were due to complications of preterm birth; it is the leading cause of death amongst neonates (death in the first 28 days of life) [4].

The WHO estimates are an important resource for assessing the burden of preterm birth at global, regional and national levels, and how that burden is changing over time. Also, they aid development and implementation of health policies, inform resource allocation in health systems, and can be used to assess the impact of interventions. The estimates are also an important tool in raising awareness of preterm birth as an important

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global public health issue. Two systematic analyses of preterm birth estimates have been published previously [5, 6]. The most recent estimates were published in 2012 (covering data for the period 1990–2010) by Blencowe and colleagues [6]. They estimated that 14.9 million babies (uncertainty range 12.3–18.1 million) were born preterm in 2010, accounting for 11.1 % of all live births worldwide. In the 65 countries with reliable time trend data for preterm birth, 62 countries had increasing rates from 1990 to 2010. However, these preterm birth estimates now require updating, in light of new data and continued refinements in statistical modelling methods.

The aim of this study is to develop national, regional and global estimates of preterm birth for all WHO Member States, for the period 1990–2014. This protocol describes the methods that will be used to identify and analyse all eligible data on preterm birth.

The objectives are:

1. To conduct a systematic review of all available data on preterm birth rates;
2. To critically appraise and synthesize eligible data, and conduct modelling to develop estimates of levels and trends of preterm birth rates at national, regional and global levels; and
3. To disseminate preterm birth estimates, in order to inform WHO Member States and other entities in the development of public health programmes and policies.

Concepts and definitions

The International Statistical Classification of Diseases and Health Problems, 10th revision (ICD-10) [7] uses the WHO definition of preterm birth, namely: “All births before 37 completed weeks of gestation or fewer than 259 days since the first day of a woman’s last menstrual period” [1]. The WHO definition does not define a lower gestational age limit for reporting; ICD-10 advises inclusion of all live births (regardless of gestational age).

Preterm birth can be further sub-divided based on gestational age:

- Extremely preterm (<28 completed weeks of gestation)
- Very preterm (28 - <32 weeks completed weeks of gestation)
- Moderate preterm (32 - <34 completed weeks of gestation)
- Late preterm birth (34 - <37 completed weeks of gestation)

WHO recommends reporting the preterm birth rate using the following indicator (Table 1), which will be the primary outcome for these estimates.

Table 1 WHO preterm birth rate indicator

number of liveborn preterm births (singleton or multiple)
number of live births (singleton or multiple)

Factors affecting standardization, measurement and comparison of the live preterm birth rate

Preterm birth includes both spontaneous preterm birth and provider-initiated preterm birth [8]. Spontaneous preterm birth includes both women in spontaneous preterm labour with intact membranes, and women with preterm prelabour rupture of membranes. Provider-initiated preterm birth includes women in whom the preterm delivery is initiated (either by induction of labour or caesarean section) for maternal or fetal indications. While it is often stated that approximately 20–30 % of preterm births are provider-initiated [8, 9], this can vary greatly between countries, and is significantly lower in many lower-income countries [10].

The pathophysiology of spontaneous preterm birth is not fully understood and several pathways have been identified [8]. While many socio-demographic, nutritional, medical, obstetric, biological and environmental factors increase the risk of preterm birth, many women who deliver preterm who do not have a clear risk factor.

Developing estimates is further complicated by several factors that can impede accurate preterm birth data measurement, estimation and comparison:

- The risk of preterm birth can be higher in some disadvantaged sub-populations (including poor, uneducated, rural-dwelling women or other minorities) where data collection may be more limited and/or facility-based births are less common;
- Misclassification of live births, stillbirths and neonatal deaths can also impact on accurately recording the liveborn preterm birth rate. As the risk of stillbirth is higher in earlier gestation, measuring the liveborn preterm birth rate can underestimate the total preterm birth burden; [11]
- National differences in the definition of preterm birth (for example, using live births or total births as the denominator, and different gestational age thresholds for defining preterm birth cases), and the relevant lower gestational age boundary for registration can complicate comparisons;
- Similarly, countries with a lower gestational age boundary for birth registration (i.e. viability) will capture a larger absolute number of births and preterm births. However, this can also potentially improve preterm birth registration rates at higher gestational ages [6].
- Gestational age (GA) estimation error is also an important factor. Generally, the later in pregnancy a

GA estimate is made, the wider the uncertainty of that estimate. Routine early pregnancy ultrasound with fetal biometric measurements is considered the “gold standard” for gestational age assessment [12]. However, other methods such as calculation from date of last menstrual period (LMP), symphysis-fundal height measurement, postnatal examination of the newborn, or use of birthweight as a gestational age surrogate are often used in resource-limited settings. Many countries report the use of “best obstetric estimate” of gestational age, using a combination algorithm of ultrasound and LMP [13].

Methods

Overview

There are two broad categories of preterm birth data available:

1. Routinely collected birth data, available from national Ministries of Health or statistical offices (civil registration vital statistics); or
2. Data from published research studies

For this study, high-quality, civil registration vital statistics (CRVS) data is the preferred data source. Civil registration is defined by the United Nations as the “continuous, permanent, compulsory and universal recording of the occurrence and characteristics of vital events [...] pertaining to a population” [14]. However, for many countries, CRVS data on preterm birth will be incomplete, of poor quality or not available [15]. In countries with absent or limited CRVS data, data from research studies will be required.

While reproductive health surveys may use population-based random sampling and have large sample sizes, they generally rely on maternal recall and knowledge of preterm birth, and hence may have poor accuracy and limited utility. Conversely, facility-based studies, particularly in settings where early antenatal care participation is high and obstetric ultrasound is available, may have greater accuracy in estimating GA and diagnosing preterm birth, however they often have smaller sample sizes and may not be representative of the general population. Consequently, it is difficult to ascertain whether certain data sources or study designs are more useful, or should supersede, other sources. Initially, we intend to be over-inclusive (in terms of study designs) and conduct necessary exploratory analyses of all included data, to explore the quality, representativeness and utility of identified data. This may result in later exclusion of certain data sources.

Following the identification and extraction of relevant data, statistical analysis and modelling will be completed to develop estimates of levels of preterm birth at global, regional and national levels, with trends at national level where sufficient data is available. The methodology and

preliminary estimates will then be reviewed by a technical advisory group (TAG) (an independent group of experts in obstetrics, neonatology, statistics and preterm birth research). The TAG will advise if any modifications are required. As per WHO standards in developing official estimates, we will also conduct a country consultation process, whereby WHO Member States are invited to review their preliminary estimates and submit any additional data not identified in the search. From this, final estimates will be developed and disseminated. This protocol has been prepared according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols (PRISMA-P) 2015 statement [6].

Eligibility criteria

For searches of CRVS and study data, the following eligibility criteria will be used:

Population

Liveborn neonates (singleton and/or multiple). Data reported using a related or similar definition of preterm will also be included. This includes preterm birth for all births (rather than live births only), singletons only, non-malformed fetuses only, or <36 weeks gestation. Women, pregnancies or newborns of non-generalizable sub-populations (such as those with specific medical or obstetric complications only, women or newborns using speciality services, selected sociodemographic groups, sub-groups based on maternal age or otherwise high-risk or selected populations) will not be included. Studies of low-risk populations only will be included.

Setting

Data from national or subnational level (including population-based, community-based and facility-based data) for the 194 Member States of WHO [16] will be considered for inclusion.

Study design

Any study design capable of producing usable data on preterm birth will be eligible for inclusion (e.g. surveys, cross-sectional studies, interventional studies) regardless of the context or the setting (e.g. nationwide, facility-based). Conference abstracts will not be included, due to insufficient data.

Outcomes

- Primary outcome:
 - Preterm birth rate (in all live births, according to the WHO definition)
- Secondary outcomes:

- Preterm birth in all births (liveborns and stillborns)
- Extremely preterm (<28 completed weeks)
- Very preterm (28 - <32 completed weeks)
- Moderate preterm (32 - <34 completed weeks)
- Late preterm birth (34 - <37 completed weeks)
- Spontaneous and provider-initiated preterm birth (<37 completed weeks)

Timeframe

All available data on preterm birth from 1990 to 2014.

Languages

No language restriction will be applied.

Sample size

There is no established method for defining a minimum sample size per data source for the development of global estimates. Previous preterm birth estimates have used cut-offs of 50 births [6] or 200 births [5] for inclusion; the 2012 estimates also used a cut-off of data obtained over ≥ 12 months [6]. For these estimates, a lower limit of 500 births (without time restriction) was selected as a cut-off by consensus of the working group, based on the following rationale:

- Smaller studies may be more susceptible to bias (eg: selection bias);
- Based on the 2012 estimates [6], it is likely that or more covariates will be required to estimate the preterm birth rate. Assuming a minimum of ten preterm birth cases per covariate, 50 preterm birth cases would be needed. Assuming a preterm birth rate of approximately 10 %, this equates to 500 births in total per dataset.

Classification of countries for assessing reliability and quality of available data

Different global estimates have used different methods of categorizing or stratifying countries on the basis of available data [6, 17, 18], depending on the outcome of interest. For example, previous maternal mortality estimates have used a three-level system for categorizing countries on the basis of the quality of mortality data reporting [18]. However, birth registration levels are generally higher than those of death and cause-of-death registration [19]. Classifying countries on the basis of cause-of-death completeness is probably not an appropriate proxy for the capture of data related to preterm birth.

For the purposes of developing preterm birth estimates, high-quality CRVS data on births should have both reasonably high coverage and completeness, as well as reporting the necessary data to determine the preterm

birth rate and the method/s of gestational age assessment. However, lower-quality CRVS data on preterm births may still be useful as an input for statistical models.

The WHO Global Health Observatory reports national estimates of civil registration coverage of births [20]. This country level indicator is derived from assessments of civil registration systems, and/or from population-based household surveys that report on proportion of births registered. The latest World Health Statistics Report (2015) [21] also reports on this indicator (for countries where data is available) based on data from the period 2007 to 2013. This indicator will be used as a proxy for identifying countries likely to have higher-quality CRVS data for preterm births for the period of interest (see Table 2 below). For countries where data is not available, we will consult with relevant WHO technical staff to inform correct categorization.

We plan to classify all WHO Member States into Groups A, B and C, on the basis of: whether CRVS data is available on preterm birth, the coverage of the civil registration system for births, and the volume of the CRVS preterm birth data available. Hence:

- Group A: Countries with CRVS birth registration coverage is over 80 %, and CRVS preterm birth data is available for ≥ 50 % of years from 1990 to 2014 inclusive;
- Group B: Countries with CRVS birth registration coverage from 60 to 80 %, and/or CRVS preterm birth data is available for < 50 % of years from 1990 to 2014 inclusive (or otherwise ineligible for Group A);
- Group C: Countries with CRVS birth registration coverage below 60 % or unknown, and/or no CRVS data for preterm birth is available (or otherwise ineligible for Group A and B).

The overview of this categorization is provided in Table 3. In some instances, expert judgment from WHO technical staff may be used to further inform correct categorization. Countries in Group A will be considered as having high-quality data for preterm birth, and no further searching will be conducted (i.e. CRVS data only will be used for these countries). For countries in Groups B

Table 2 Civil registration coverage of births for 194 WHO Member States [21]

Civil registration coverage of births (%)	Number of countries (%)
>80 % coverage	126 (64.9 %)
60 % - ≤ 80 % coverage	23 (11.9 %)
<60 % coverage	29 (15.0 %)
No data	16 (8.2 %)
Total	194 WHO Member States

Table 3 Categories and criteria for Groups A, B and C in WHO preterm birth estimates

		WHO Member States		
		Group A country	Group B country	Group C country
Quality Criteria	Source	Specific criteria		
1. Preterm birth data available	Assess available CRVS data	CRVS data for preterm birth are available, ie: Preterm birth rate is given or can be calculated	CRVS data for preterm birth are available, ie: Preterm birth rate is given or can be calculated	No CRVS for preterm birth available, or CRVS data available but country does not otherwise meet Group A or B criteria
2. Quality of civil registration system for births	Civil registration coverage of births (%)	CRVS coverage for births >80 % [20] (or country can be otherwise classified as having high coverage for birth registration)	CRVS coverage for births is 60 % - <80 % [20]	CRVS coverage for birth data is <60 % or unknown [20]
3. Volume of CRVS data	Assess available CRVS data	• ≥500 births • Commencement date of data collection after 1/1/1990 • End date of data collection is before 31/12/2014 • Number of years where preterm data available is >50 % for the period 1990 to 2014 inclusive (i.e. CRVS data available for at least 13 years)	• ≥500 births • Commencement date of data collection after 1/1/1990 • End date of data collection is before 31/12/2014 • Data for any year/s between 1990 to 2014 inclusive (but does not meet Group A criteria)	• No CRVS data on preterm birth available, or • CRVS data on preterm birth available, but country does not otherwise meet Group A or Group B criteria^a
Data sources for development of estimates				
Data sources:		CRVS data only to be used	Conduct systematic review of published studies to identify additional data sources	Conduct systematic review of published studies to identify additional data sources

^aCountries that have CRVS data for preterm birth, but CRVS coverage for birth data is <60 % or unknown, will be considered Group C countries

and C, available CRVS data will be used as inputs for statistical models, however further searching (systematic review of available literature) will be conducted for these countries. It is envisaged that some CRVS data may be of such poor quality that it cannot be used, and will be excluded.

The systematic review of data from Group B and C countries will consider both interventional and observational designs (case-control studies will be specifically excluded) presenting original quantitative data on preterm birth. If intervention studies are included, all arms will be considered for inclusion. However, if the preterm birth rate is significantly different between arms (or the significance is unknown), only the control arm/s will be used.

Search strategy and classification of countries

CRVS data will be obtained through online searching of national Ministry of Health and national statistical office publications and datasets for every WHO Member State. A review of references from the 2012 WHO preterm birth estimates activity [6] will be used to supplement this search, as will eligible data from the country consultation (see below).

For the systematic review of published studies, the following databases will be searched: Medline, EMBASE, Popline, WHO Global Health Library (including regional and global indexes), CINAHL, PsychInfo, and the

Cochrane Central Register of Controlled Trials (CENTRAL). Citations from previous systematic reviews of levels and trends of preterm birth will also be reviewed [5, 6]. A *pro forma* email specifying our analysis objectives and inclusion criteria will be developed and circulated to further identify data. We will contact key stakeholders working in each country and in maternal and neonatal health research networks in countries where little or no data is available, in order to further identify additional unpublished datasets (if available). Given the population size of China, and the lack of a national CRVS data on preterm birth, we will conduct a separate search of Chinese language health and medical databases, using the same protocol.

Screening, data selection and collection process

Two reviewers will independently screen all citations (title and abstract) identified through the searches, to assess for potential eligibility. In the case of disagreement or where the information is not sufficient for decision on inclusion/exclusion, the article will be included for full text review. Full texts of potentially eligible studies or sources will be retrieved and independently assessed for inclusion by two reviewers. Any discrepancies will be resolved by discussion and consensus by the two reviewers or through consultation with a third reviewer. Where citations are excluded at this step, the reason for exclusion will be documented.

We will develop a standard data extraction form that will be pilot tested against both CRVS and study data on preterm birth. Data extraction from the full text articles will be done using this standard form via an online data management database, completed independently by two reviewers with the results compared. In the event of disagreement, discrepancies will be resolved by discussion and consensus, or by consultation with a third reviewer. All data inclusion and exclusion will be reported according to the PRIMSA checklist.

Extracted data will include: country, data source, design, time period, definition and methods used, range of gestational age used, method of GA assessment, as well as prevalence and incidence data on preterm birth (according to primary and secondary outcomes) and covariate data (see below).

Assessing quality of data sources

In this review we will potentially include data from a range of study designs. However there is currently no established tool for standardized assessment and comparison of quality across multiple study designs. To this end, the WHO abortion estimates working group developed a data quality assessment tool, with the aim of “systematic, quantitative, and efficient differentiation of studies into different quality levels” (Tuncalp O, personal communication). The quality of data sources was assessed using a five-point checklist, adapted from items within the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. Items were selected to assess quality in distinct sections of the data source, to be relevant across a range of study designs, and to be manageable in terms of time required to conduct the quality assessment.

This has been reviewed and adapted for use in these estimates. The checklist includes the following five domains:

1. Eligibility criteria for the participants in the study are provided;
2. Method of gestational age assessment (i.e. measurement of the primary outcome) are provided;
3. Characteristics of study participants (e. g. demographic, clinical, social) are provided;
4. The numbers of all outcome events/summary measures are reported;
5. Authors discuss relevant sources of potential bias and/or imprecision in the limitations/discussion.

Each item will be rated as met (1 point) or unmet/not clear (0 point). Hence, for a given data source a maximum score of 5 is possible. Reviewers that extract data will score the data source based on the above criteria.

Scores will be imputed by the reviewer into the data extraction spreadsheet. In the case of disagreement, agreement will be reached through consensus, or through engaging a third reviewer.

Once completed, the score distribution will be assessed and reported descriptively. Data sources with the lowest scores will be re-evaluated; we will consider excluding data sources on the basis of low quality. Sensitivity analyses may also be used. These scores will not be used for weighting in modelling.

Regions

Regions will be defined and reported according to multiple official groupings, including United Nations Regional Groups, WHO Regions, Sustainable Development Goal Regions, World Bank Regions and Income Groups, and other UN agency regional groupings (UNFPA, UNICEF, UNDP).

Covariates

In countries with little or no preterm birth data available, modelling the preterm birth rate on the basis of covariates will be required. Candidate predictors have been preliminarily identified based on clinical relevance, known risk factors for preterm birth and covariates identified in previous preterm birth estimates. These are:

- Neonatal mortality rate
- Low birthweight rate
- Caesarean section rate
- Multiple birth rate
- HIV prevalence rate (women 15–49 years old)
- Malaria rate (notified cases of malaria per 100,000 population)
- Proportion of women receiving four or more antenatal care visits
- Mean adult female BMI
- Gross Domestic Product (GDP) per capita
- Total fertility rate
- Female literacy rate
- Human Development Index
- Maternal mortality ratio (MMR)
- Adolescent pregnancy rate
- Skilled birth attendance rate
- Facility delivery rate
- Gestational age range used by countries (for live birth and preterm birth registration)

We aim to identify and extract available data on these covariates from individual studies included in the systematic review. This will allow modelling using study-specific covariate values. Additionally, it will permit a better description of the study database, identify potential selection biases (i.e. selected populations) in identified studies,

and also facilitate possible sensitivity or secondary analyses (if required). However, it is unlikely that individual studies will contain data on all the covariates identified above. We identified a shortlist of covariates where data is likely to be available, which will be extracted from individual studies:

- Neonatal mortality rate
- Low birthweight rate
- Caesarean section rate
- Adolescent pregnancy
- HIV rate (for the study population)
- Malaria rate (for the study population)
- Proportion of women receiving four or more antenatal care visits

Where study-specific covariate data are not available, national estimates of covariates from the most comprehensive United Nations sources will be used.

Result

Statistical analysis and modelling

In the primary analysis all data (regardless of definition of preterm birth) will be used. The WHO definition for preterm birth rate will be the reference definition in the analysis and for the presented results. Some data sources may use alternative definitions of preterm birth, in which case proportionate adjustment of the regression models will be explored.

We hypothesize that the magnitude of associations between covariates and preterm birth are likely to vary by region. Hence, we will develop region-specific models (described below). However, once the database is assembled, we will conduct exploratory analyses to assess whether sufficient data exists to permit development of these region-specific models and if not, a global model will be developed.

For Group A countries, only CRVS data will be included. For Group B & Group C countries, both CRVS and study data will be included. All included data will be analysed as described below (regardless of country group). The predicted preterm birth rate for 2014 at national, regional and global levels will be presented. For those countries with sufficient data, trends will also be presented (see below). All analyses will be conducted using Stata 14.

Preparation for analysis

To facilitate the development of models, we will obtain estimates of country level covariates from comprehensive, publicly available United Nations sources. If country covariate data is missing for some countries and/or timepoints, these will be imputed based on separate regression models. Where available, data on selected covariates will

also be extracted directly from data sources. If a data source-specific covariate value is available, this will be used preferentially in the models over covariates from national estimates.

Phase 1: modelling

In the first phase, the preterm birth outcome will be modelled using a two-level (country and data source) linear mixed regression model, including random country-specific intercept and slope. The model will include time, data source characteristics and covariates. Inclusion of covariates will be based on model fit parameters (BIC, AIC) by removing one covariate at a time and refitting the model. If the model is improved by removing the covariate, the covariate will be excluded. Linearity will be assessed graphically per country. For those regions that contain countries where the relationship between covariates and the preterm birth outcome is clearly not linear, a spline function or log transformation will be considered. In this phase, no preterm birth outcome data will be imputed for missing countries and/or timepoints. Hence, the regional models will only be based on available data. Restricted maximum likelihood estimation (REML) will be used to develop the regional models, and country random effects will be calculated by best linear unbiased predictor (BLUP).

Phase 2: prediction of preterm birth rate in 2014

The predicted preterm birth rates in 2014 will be calculated based on the regional models, using country-specific random coefficients and covariate data. Regional and global predictions for 2014 will be calculated based on the national estimates, weighted using number of live births. Predictions for countries providing no preterm birth outcome data will be based on the regional average (i.e. random coefficients assumed to be zero) adjusted according to country covariates. Standard errors for regional and global predictions will be calculated from country level standard error. For countries providing no preterm birth outcome data the standard error will be assumed to be of the same level as the country having the largest standard error in the region.

Phase 3: presentation of results

For all countries, regions and globally the 2014 predicted preterm birth rate will be presented together with 95 % confidence intervals. For each country, both the reported and the predicted preterm birth outcome data will be graphed from the first year where data was available to 2014. Both continuous predictions and means over 5 year periods will be presented. For countries where no preterm birth outcome data was identified, only the 2014 predicted value will be presented.

Country consultation

Following the development of the preliminary estimates, WHO will conduct an official country consultation. WHO Member States (via their focal points) will be invited to confidentially review the methodology and preliminary estimates for their country. They will also be invited to submit additional data that may not have been identified through the searches. If additional data is identified, it will be reviewed and included if eligible. Subsequently, the models will be re-fit including these new inputs.

Project management

HRP/RHR will lead the technical activities related to data search and synthesis, as well as country consultations, in order to produce updated official WHO estimates. A Technical Advisory Group (TAG) will be established to provide oversight and technical input on the development of these estimates. The TAG will comprise a group of international experts on preterm birth estimates and modelling techniques.

Discussion

This study will be used to generate estimates of rates and trends of preterm birth at national, regional and global levels for 1990 to 2014. These estimates are a useful resource for public health providers, researchers and policymakers, in order to advance understanding the burden of preterm birth, raise awareness and to better target and evaluate public health programmes and track progress.

We invite feedback on the methodology described, and call on the public health community to submit unpublished yet potentially eligible data for consideration, to WHO via pretermbirth@who.int.

Abbreviations

BLUP, best linear unbiased predictor; BMI, body mass index; CRVS, civil registration and vital statistics; GA, gestational age; GDP, gross domestic product; HIV, human immunodeficiency virus; HRP, UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction; ICD, International Classification of Diseases; LMP, last menstrual period; MMR, maternal mortality ratio; PTB, preterm birth; RHR, Department of Reproductive Health and Research; TAG, technical advisory group; UNDP, United Nations Development Programme; UNFPA, United Nations Population Fund; UNICEF, United Nations Children's Fund; WHO, World Health Organization

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Availability of data and materials

When the WHO estimates are published, the primary analysis will contain additional supporting data on development of the estimates. Furthermore, data will be made freely available in a public repository.

Authors' contributions

This activity was initially conceptualized by JPV and AMG. The first draft of the protocol was developed by JPV, SC, KW, PL, MP. All named authors

participated in an in-person meeting to review and revise the conception and design of this activity, and contributed to the development of the final manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

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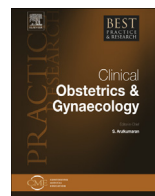




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Ending preventable maternal and newborn deaths due to infection

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Over 300,000 maternal deaths occur each year, 11% of which are thought to be due to infectious causes, and approximately one million newborns die within the first week of life annually due to infectious causes. Infections in pregnancy may result in a variety of adverse obstetrical outcomes, including preterm delivery, pre-labor rupture of membranes, stillbirth, spontaneous abortion, congenital infection, and anomalies. This paper reviews the burden of disease due to key infections and their contribution to maternal, perinatal, and newborn morbidity and mortality, as well as key interventions to prevent maternal and newborn deaths related to these infections. Research needs include more accurate clinical and microbiologic surveillance systems, validated risk stratification strategies, better point-of-care testing, and identification of promising vaccine strategies.

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Scope of the Problem

Over 300,000 maternal deaths occur each year, 11% of which are thought to be due to infectious causes, and approximately one million newborns die within the first week of life annually due to infectious causes [1,2]. Furthermore, around 2.6 million stillbirths occur each year worldwide, with major causes being infections, including chorioamnionitis, syphilis, and malaria [3]. Over 98% of all of these deaths occur in low- and middle-income countries (LMIC).

Infections in pregnancy may result in a variety of adverse obstetrical outcomes, including preterm delivery, pre-labor rupture of membranes, spontaneous abortion, congenital infection, and anomalies. The types of infections span the microbial spectrum, including bacterial, viral, and parasitic diseases. The aims of this review are to (1) discuss what is known about the contributions of key individual infections to maternal, perinatal, and newborn mortality and morbidity and (2) review interventions to prevent maternal and newborn deaths related to these infections and their effectiveness.

Human Immunodeficiency Virus (HIV)

Burden of Disease

The estimated number of pregnant women living with HIV globally exceeds 1.5 million [4], the majority in sub-Saharan Africa. The health of a woman with HIV in pregnancy and beyond depends on her sustainable access to antiretroviral therapy (ART), as well as other medications for treatment and prevention of opportunistic infections. A recent population-based open cohort study in rural Uganda found that life expectancy in women living with HIV increased by 22.9 years between 2000 and 2002 and 2009 and 2012, coinciding with introduction of ART in 2004 [5]. Perinatal transmission from an HIV-infected woman to her fetus or infant is the leading cause of pediatric HIV infections, with approximately 220,000 new HIV infections among children in 2014; however, this is a reduction of 58% from the number of infections in 2000, largely due to increased access to antiretroviral medications during and after pregnancy: as of June 2015, 73% (68–79%) of pregnant women living with HIV had access to antiretroviral medicines to prevent transmission of HIV to their babies [6].

Mother-to-child transmission

Mother-to-child transmission (MTCT) can occur during pregnancy, labor, delivery, or with breast-feeding and in the absence of any intervention transmission rates ranging from 15% to 45%. In high-resource settings, MTCT rates as low as 0.46% have been achieved with the use of effective combination of ART started early in pregnancy or prior to conception, attainment of undetectable HIV viral load, and avoidance of breastfeeding [7]. Cesarean section is recommended at 38 weeks of gestation only if the HIV viral load is >1000 copies/mL near the time of delivery [8]. In the US, it is now recommended that all individuals with HIV initiate ART regardless of the CD4 cell count, based on increasing evidence that earlier initiation of ART reduces morbidity due to the number of non-acquired immune deficiency syndrome (AIDS)-defining conditions, improves survival, and substantially reduces sexual transmission [9].

In lower-resource countries, perinatal transmission can be reduced below 5% with currently available interventions. In 2013, World Health Organization (WHO) released Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection in limited resource settings [10]. All pregnant women should have HIV testing and counseling on the first antenatal visit and retesting should be considered in the third trimester or peripartum, especially in settings of generalized epidemics. Key recommendations relevant to treatment of pregnant women are summarized below:

- All pregnant and breastfeeding women with HIV should initiate triple antiretroviral drugs (ART), with those meeting the treatment eligibility criteria continuing with lifelong ART. For programmatic and operational reasons, particularly in generalized epidemics, lifelong ART is preferred for all pregnant and breastfeeding women, regardless of the CD4 count (Option B+). With Option B+, ART is stopped after cessation of breastfeeding in women who do not meet the eligibility for treatment.

- The recommended first-line regimen is a combination of efavirenz (EFV) + lamivudine (3TC) or emtricitabine (FTC) + tenofovir. Recent evidence from systematic reviews is reassuring regarding the safety and efficacy of EFV in pregnancy [11].
- HIV-exposed infants should be exclusively breastfed for the first 6 months of life, with introduction of complementary foods thereafter, and continued to be breastfed for the first 12 months of life; breastfeeding should stop only when there is an adequate and safe diet. The benefits of breastfeeding in preventing diarrhea, pneumonia, and malnutrition [12] have been shown to outweigh the risk of HIV transmission in low-resource settings.
- With Option B+, infants who are breastfeeding should receive 6 weeks of infant prophylaxis with nevirapine once daily; infants receiving replacement feeding should receive 4–6 weeks of nevirapine or azidothymidine.
- Cesarean section is recommended in resource-limited settings *only* for standard obstetric and other medical indications.

Pregnancy may also be a time of increased risk for HIV acquisition [13], and acute infections in pregnancy carry a greater risk for perinatal transmission, both because of missed opportunities for diagnosis and because of higher HIV viral loads with acute infection [14]. Providers should have a high index of suspicion for acute infection with compatible clinical signs and symptoms and in women known to be at increased risk.

Tuberculosis (TB) and HIV

TB is the leading cause of HIV-associated mortality globally, accounting for one out of every five HIV-related deaths. The risk of developing TB is 30 times higher among people living with HIV than among people who do not have HIV infection and can occur at any CD4 count [15].

Pregnant women living with HIV who have TB are three times more likely to die than women who have TB alone [16]. When a pregnant woman is co-infected with HIV, TB also doubles the risk of vertical transmission of HIV to the unborn child [17] and co-infection may increase the risk of congenital TB or postpartum TB transmission through airborne exposure [18]. Other adverse outcomes include increased risk for preterm delivery, low-birth weight (LBW), and a six-fold increase in perinatal deaths [19].

All pregnant women living with HIV in TB-endemic areas should be screened at each antenatal visit using the WHO-recommended symptom algorithm: current cough, fever, night sweats, or weight loss (or poor weight gain in pregnancy) [10]. Women with any one of these symptoms should be evaluated for TB. Xpert MTB/RIF on sputum should be used as the initial diagnostic test in individuals suspected of having HIV-associated TB or multidrug-resistant TB [20]. Smear-negative pulmonary TB is common in HIV-infected pregnant women and therefore smear microscopy alone has limitations in diagnosis. Extrapulmonary TB is more common in pregnancy and should be considered when women have atypical signs or symptoms, such as enlarged lymph nodes [21].

TB treatment consists of a standardized regimen of antibiotics taken for at least six months, irrespective of HIV status. Completing TB treatment is critical to reducing mortality and avoiding the development and spread of drug-resistant TB. ART should be initiated as soon as possible, no later than eight weeks after initiation of TB treatment [22].

Isoniazid preventive treatment (IPT) and ART given together can reduce the risk of TB among people living with HIV by up to 97% [23]. Pregnant women who do not report any of the symptoms on screening are unlikely to have active TB and should be offered IPT for at least six months [24].

Malaria

Malaria is caused by an infection with protozoan parasites of the genus *Plasmodium* (*P. falciparum* (cause of most maternal illness), *P. malariae*, *P. ovale*, *P. vivax*, and *P. knowlesi*) and transmitted by female *Anopheles* mosquito vectors in tropical and subtropical areas. The highest transmission occurs in sub-Saharan Africa. In areas where populations are continuously exposed to a high frequency of malarial inoculation, partial immunity to clinical disease and a reduced risk of developing severe malaria are

generally acquired in early childhood. In other areas, such as much of Asia and Latin America, the intensity of malaria transmission fluctuates widely by season and year, which retards the development of immunity so that people of all ages suffer from acute clinical malaria, with a significant risk for progression to severe malaria if untreated. Maternal mortality attributable to malaria is as high as 17.6–23% in hospital and community studies [25] and 75,000–200,000 neonatal deaths yearly are attributable to malaria [26,27].

In sub-Saharan Africa, there are 50 million women living in malaria-endemic areas, who become pregnant each year [28], and the median prevalence of maternal malaria is 28 percent [25].

Malaria and Pregnancy

The incidence of malaria is higher during pregnancy compared with before or after pregnancy [29]. Where levels of acquired immunity are high, malaria in pregnancy is usually asymptomatic or with mild nonspecific symptoms, but parasites may be present in the placenta and contribute to maternal anemia and adverse fetal effects, even in the absence of documented peripheral parasitemia. In these settings, the adverse effects of malaria in pregnancy are most pronounced in the first pregnancy [30]. In lower transmission settings, where there is little acquired immunity, malaria in pregnancy is associated with anemia, increased risk of severe malaria in the mother, and increased risk of severe adverse fetal effects and can affect women regardless of the number of pregnancies.

Effective treatment in the early stages of malaria should result in rapid and full recovery; however, if treatment is inadequate or delayed, severe malaria can develop quickly, and if untreated it is fatal in the majority of cases. Compared with nonpregnant women, pregnant women experience more severe disease, more hypoglycemia, and more respiratory complications (pulmonary edema, acute respiratory distress syndrome) [31].

In endemic regions, maternal malaria may account for one-quarter of LBW infants, and this risk is highest in the first pregnancy [25,27]. Placental malaria increases the odds of both LBW and stillbirth twofold [32,33] and maternal malaria increases the risk of miscarriage up to threefold [34]. Congenital malaria from transplacental transmission can occur but is lower in mothers with immunity from prior exposure. [35] Infants with congenital malaria generally present at 2–8 weeks of age with irritability, fever, vomiting, diarrhea, and poor feeding. Anemia, thrombocytopenia, and hyperbilirubinemia are common [25].

Pregnant women with HIV may be at higher risk for malaria acquisition, placental malaria, higher parasite densities, and more severe clinical disease, and after delivery women with HIV and malaria are at increased risk for anemia compared with HIV-seronegative women with or without malaria. Co-infection with HIV and malaria is also associated with an increased risk of adverse perinatal outcomes and may increase the risk of perinatal HIV infection [36–38].

Diagnosis

Malaria should be suspected clinically primarily based on fever or temperature $\geq 37.5^{\circ}\text{C}$ with no other obvious cause. Unfortunately, the signs and symptoms of malaria are nonspecific (e.g., headache, myalgias, fatigue, nausea, vomiting, abdominal pain, and worsening malaise), and there is no combination of signs and symptoms that increases specificity. Suspected malaria should be confirmed with a parasitological test (microscopy or rapid diagnostic test) and the results should be available within a short time (<2 h) to reduce over-treatment with antimalarial drugs and improve the diagnosis of other febrile illnesses. However, in settings where timely diagnosis is not possible, antimalarial treatment should be started promptly when a diagnosis of malaria is likely. (WHO) IPT can suppress or clear existing asymptomatic infections and provide prophylaxis against possible new infections; antimalarial treatment should be started promptly when a diagnosis of malaria is likely [31].

Treatment

Resistance to antimalarial drugs is a major threat to control and eliminate malaria and is likely related to widespread inappropriate use of antimalarial drugs, inappropriate dosing, or treatment, with

greatest resistance seen with *P. falciparum*. Resistance can be prevented or slowed by combining antimalarial drugs with different mechanisms of action and full adherence to correct dose regimens. Current WHO recommendations for treatment of uncomplicated *P. falciparum* malaria are to use quinine + clindamycin in the first trimester and a recommended artemisinin-based combination therapy (ACT) in later pregnancy; although there are limited data on ACT exposure early in pregnancy, inadvertent exposure is not considered an indication for pregnancy termination [31]. *P. vivax* is the dominant malaria species outside Africa malaria and, unlike *P. falciparum*, has a dormant liver stage that causes relapses; weekly chloroquine chemoprophylaxis has been shown to substantially reduce recurrent *P. vivax* malaria in pregnancy [39]. Severe malaria should be treated with recommended parenteral artesunate without delay.

Prevention

In malaria-endemic areas in Africa, the WHO recommends implementation of intermittent preventive treatment (IPT) for all pregnant women in their first or second pregnancy with monthly sulfadoxine–pyrimethamine (SP) beginning in the second trimester, with the goal of at least three doses being received [31]. A systematic review showed reduction of LBW and placental and maternal parasitemia with three or more doses compared with two doses across a wide range of resistance to SP [40].

However, currently only around one-quarter of pregnant women in Africa receive IPT-m [41]. HIV-positive women who are taking co-trimoxazole for OI prophylaxis should not receive additional prophylaxis with SP [31].

A second preventive approach is the use of insecticide-treated bed nets (ITN); a Cochrane review of ITNs showed reduced risk of placental malaria (RR 0.79), LBW (RR 0.77), stillbirth, and miscarriage (RR 0.67) compared with the control group [42]. In a survey of pregnant women in 37 malaria-endemic countries, only 33% of the women reported having slept under an ITN the previous night [41].

Sepsis

Maternal Sepsis

Epidemiology

Several terms are used synonymously with maternal sepsis, including puerperal sepsis and maternal peripartum infection; these are defined by WHO as infection of the genital tract or surrounding tissues occurring between the onset of rupture of membranes or labor and the 42nd day postpartum in which two or more of the following are present: pelvic pain, fever, abnormal vaginal discharge, foul-smelling discharge, or delay in uterine involution [43,44].

The factors associated with increased risk of maternal sepsis can be categorized into preexisting maternal conditions and conditions occurring during labor and childbirth. Preexisting maternal conditions include malnutrition, diabetes, obesity, severe anemia, bacterial vaginosis, and Group B Streptococcus (GBS) infections. Conditions during labor and childbirth are prolonged labor, prolonged membrane rupture, internal fetal or uterine monitoring, presence of genital tract pathogens, multiple vaginal examinations, manual removal of the placenta, operative vaginal birth, and cesarean section [45,46]. Cesarean section is an important risk factor, with a five- to eightfold increased risk compared with vaginal birth [46]. Frequency is highest in preterm delivery and with preterm membrane rupture [47,48].

The three most important causes of maternal sepsis include pyelonephritis, chorioamnionitis, and endometritis [45,49]. The other causes include wound infection, mastitis, and pneumonia. The causative microorganisms causing maternal sepsis usually are polymicrobial, including aerobic (e.g., GBS, *Escherichia coli*, *Klebsiella pneumoniae*, etc.) and anaerobic bacteria (e.g., *Bacteroides fragilis*, *Peptostreptococcus* spp, etc.) [45].

Chorioamnionitis

Chorioamnionitis is the most common obstetric cause of maternal sepsis. It is an acute inflammation of fetal membranes, amniotic fluid, and/or placenta and is associated with 20–40% of early neonatal sepsis and pneumonia [50]. It is most often caused by ascending infection from the lower

genital tract and less commonly through hematogenous/transplacental spread or direct inoculation through invasive procedures.

The key clinical findings include fever, uterine tenderness, maternal tachycardia ($>100/\text{min}$), fetal tachycardia, and purulent or foul amniotic fluid. Fever is present in almost all cases of clinical chorioamnionitis and is considered the essential criterion for clinical diagnosis [51]. Maternal tachycardia ($>100/\text{min}$) and fetal tachycardia ($>160/\text{min}$) are also common, reported 40–80% of cases [52]. Chorioamnionitis may also be subclinical, which may manifest as preterm labor (PTL) or premature rupture of membrane (PROM), especially when preterm. Chorioamnionitis is associated with increased risk of labor abnormalities, uterine atony, postpartum hemorrhage, and endometritis [53]. Leukocytosis is very common but nonspecific as an isolated finding. Amniotic fluid culture, although considered the “gold standard,” is of limited value because of the length of time for results, difficulty in obtaining sterile specimens, and high frequency of negative results [52,54]. Inflammatory markers hold promise for early and more rapid diagnosis [55].

Treatment

Broad-spectrum antibiotics should be started promptly when a diagnosis of chorioamnionitis is made, which have been associated with significantly reduced maternal and neonatal morbidity [52].

Antibiotics should be effective against beta-lactamase-producing aerobes and anaerobes; the most common regimen is ampicillin and gentamicin, but the combination of gentamicin and clindamycin has been shown to be superior to penicillins in the treatment of postpartum endometritis [56]. The optimal duration for continuing antibiotic therapy postpartum has not been determined conclusively, although data from small randomized and observational studies suggest that only one additional dose is needed [57]. There is no evidence that oral antibiotics are needed after discontinuation of parenteral therapy [58]. Cesarean section is not indicated for chorioamnionitis unless there are other obstetric indications. Maternal fever has been shown to have an independent association with neonatal encephalopathy [59], supporting the adjunctive use of antipyretics.

Neonatal Sepsis

Neonatal sepsis is a systemic infection due to a microbial pathogen in the first 28 days of life and is an important cause of morbidity and mortality among newborns. Early-onset sepsis is generally defined as the onset of symptoms before 7 days of age and late-onset sepsis is defined as the onset of symptoms at ≥ 7 days of age. Neonatal sepsis may include meningitis, which occurs in as many as 15% of neonates with bacteremia, pneumonia, or involvement of other organs. Important risk factors for early-onset infection include maternal chorioamnionitis [60], intrapartum maternal fever $> \text{or} = 38^\circ\text{C}$, preterm delivery (<37 weeks gestation), maternal group B streptococcal colonization, and membrane rupture ≥ 18 h, which increases the risk 10-fold [61]. Early-onset infection is usually due to vertical transmission by contaminated amniotic fluid or during vaginal delivery from bacteria in the mother's lower genital tract [62]. Late-onset infections may be caused by initial neonatal colonization evolving into infection or from direct contact with care providers or environmental sources. Metabolic factors (e.g., hypoxia, hypothermia, acidosis) may increase risk and severity of neonatal sepsis by disrupting the neonate's immunologic responses [63].

Epidemiology

The overall incidence of neonatal sepsis ranges from one to five cases per 1000 live births in the US [64,65]. In South Asia, sub-Saharan Africa, and Latin America in 2010, there were 1.7 million cases of neonatal sepsis [66]; approximately half a million neonatal deaths annually are due to neonatal sepsis [67]. Infection rates increase with decreasing gestational age. The incidence of early-onset sepsis has decreased in settings where intrapartum antibiotic prophylaxis (IAP) is used, primarily related to a reduction in GBS infections [64,68].

GBS and *Escherichia coli* (*E. coli*) are the most common causes of both early- and late-onset sepsis; [69]. In a recent systematic review, Africa was estimated to have the highest incidence of GBS in infants worldwide [70]. *E. coli*, *K. pneumoniae*, and *Staphylococcus aureus* are also commonly reported pathogens in early-onset neonatal sepsis in developing countries [71,72].

Diagnosis and Management

Signs and symptoms of sepsis are nonspecific and can be subtle; therefore, recognition of risk factors and having a high index of suspicion is important. Fetal distress in labor, fetal tachycardia, meconium-stained amniotic fluid, and Apgar score ≤ 6 may be early indicators of sepsis. In the newborn, temperature instability, irritability, lethargy, respiratory symptoms, poor feeding, seizures, tachycardia, jaundice, poor perfusion, and hypotension [63] may be seen.

In low-resource countries, diagnoses are often made by health care workers without specialist training. To support a diagnosis of possible severe bacterial infections and to guide treatment, clinical algorithms have been developed and are included in the Integrated Management of Childhood Illness (IMCI) [73]. Seven clinical signs (respiratory rate $>60/\text{min}$, severe chest in-drawing, temperature $>37.5^\circ\text{C}$ or $<35.5^\circ\text{C}$, no movement or movement only on stimulation, convulsions, poor feeding) had 85–87% sensitivity and 62–75% specificity for serious possible bacterial infection in the first week of life, as compared with an experienced pediatrician's diagnosis (in some cases with supporting laboratory data) as the gold standard [74,75].

Neonates with signs and symptoms of sepsis require prompt clinical and laboratory evaluation (cultures, complete blood count, lumbar puncture) and initiation of empiric antibiotic therapy [62]. A definitive diagnosis of neonatal sepsis is established by a positive blood culture, but blood culture may be negative by up to 38 percent in infants with meningitis [62,76]. Molecular techniques may improve diagnostic ability; in addition, they have a more rapid turnaround time, require smaller volumes of blood, and are not affected by the administration of antepartum antibiotics [77].

Infants of mothers with chorioamnionitis should receive empiric treatment with antibiotics while under observation [78]. Infants appearing well with identified risk factors for sepsis should be observed for a minimum of 48 h, with consideration of more limited diagnostic evaluation based on the nature of the risk factor(s) and maternal receipt of IAP.

Infants who present with signs or symptoms of infection later than 7 days of age should also have appropriate cultures and be started on empiric antibiotic therapy. The antibiotic regimen should be started pending the culture results and should include agents active against GBS and other organisms that cause neonatal sepsis. In the US, ampicillin and gentamicin are generally the preferred regimen for both early-onset disease and community-acquired late-onset sepsis; however, local antibiotic resistance patterns must be considered and regimens may require alteration based on culture results or specific site(s) of infection.

In lower-resource settings, empirical treatment for neonatal sepsis with intravenous (IV)/intramuscular (IM) ampicillin (or penicillin) plus gentamicin for 7–10 days is recommended by WHO. Injectable coxacillin is an alternative if staphylococcal infection is suspected and a third-generation cephalosporin is a second-line therapy if there is no response after 48–72 h of therapy. In neonates born to mothers with PROM ≥ 18 h, maternal fever $\geq 38^\circ\text{C}$ before delivery, and foul-smelling amniotic fluid, neonatal treatment is recommended for 48 h with close observation [79]. IAP is recommended for women in PTL rupture of membranes [80] (WHO, Recommendations on interventions to improve preterm birth outcomes, WHO, Geneva, 2015). There is evidence for reduced antimicrobial susceptibility in pathogens causing both hospital- and community-acquired infections, threatening current empiric treatment strategies [72,81]. However, recently completed community-based clinical trials in Africa and Asia where referral was not feasible have shown that a large proportion of community-acquired infections responded clinically to gentamicin and amoxicillin [82,83]. WHO has recently launched guidelines to manage possible serious bacterial infection in neonates and young infants when referral is not possible with simplified antibiotic regimens on outpatient basis. However, critically ill neonates and young infants were not recommended to be treated on an outpatient basis [84].

Supportive care is an essential part of management, including maintaining adequate oxygenation, IV fluids, temperature and glucose regulation, normal fluid and electrolyte balance, and prevention of metabolic acidosis. Simple bedside tests are available in low-resource settings for testing glucose levels, and temperature regulation can be improved by Kangaroo Mother Care. Severely ill infants may require mechanical ventilation and vasopressor support.

Survivors of neonatal sepsis may have long-term sequelae. Approximately 20% of survivors of neonatal meningitis have severe disability and another 35% have mild-to-moderate disability [85].

Prevention of maternal and neonatal sepsis

Prevention of maternal and neonatal sepsis in all settings includes good infection control, including hand hygiene. Data from a systematic review demonstrated that there was a reduction in neonatal death, cord infection, and neonatal tetanus when the birth attendant washed her hands [86]. Topical application of chlorhexidine to the umbilical cord was associated with a 12% reduction in neonatal mortality in the community setting in a recent meta-analysis; current WHO guidelines recommend daily application of chlorhexidine to the umbilical cord stump in the first week of life for newborns who are born at home in settings with high neonatal mortality (30 or more neonatal deaths per 1000 live births) [87,88]. The use of vaginal chlorhexidine during labor was not found effective in preventing maternal and neonatal infections in a systematic review [89].

The use of prophylactic antibiotics with C-section has been associated with a decreased incidence of wound infection (RR 0.40, 95% CI 0.35–0.46), endometritis (RR 0.38, 95% CI 0.34–0.42), and serious infectious maternal complication (RR 0.31, 95% CI 0.20–0.49) [90]. There is evidence from a meta-analysis that reveals that antibiotic prophylaxis for Cesarean delivery given before skin incision, rather than after cord clamping, decreases the incidence of postpartum endometritis (RR 0.47, 95% CI 0.26–0.85) and total infectious morbidities (RR 0.50, 95% CI 0.33–0.78) [91]. The American College of Obstetricians and Gynecologists recommends that prophylaxis should be given within 60 min before the start of the cesarean delivery with a single dose of a first-generation cephalosporin or a combination of clindamycin with gentamicin in penicillin-allergic patients. Obese patients having excessive blood loss may require additional or altered dosing. No data exist to support using prophylactic antibiotics in the manual removal of placenta during cesarean or vaginal delivery [92].

In the US, the primary intervention to prevent early-onset neonatal sepsis is screening pregnant women for GBS colonization and administering IAP with GBS colonization and other risk factors. The Center for Disease Control and Prevention (CDC) recommends that all pregnant women should be screened for GBS colonization with a swab of the lower vagina and rectum at 35–37 weeks of gestation, except women who have had GBS bacteriuria during the current pregnancy or a prior infant with GBS disease, who should always receive IAP. IAP should also be given to women whose GBS culture status is unknown if delivery is at <37 weeks of gestation, amniotic membranes have ruptured for ≥ 18 hours, intrapartum temperature $\geq 100.4^\circ\text{F}$ ($\geq 38^\circ\text{C}$) is documented, or intrapartum nucleic acid amplification test (NAAT) is positive for GBS. Adequate IAP is defined as IV penicillin, ampicillin, or cefazolin given id a prior to delivery. [78] A recent meta-analysis found that IAP was associated with a significant reduction in chorioamnionitis and endometritis in women who had term or near-term membrane rupture >12 h [93]. In women with preterm premature rupture of membranes, data from recent meta-analysis found that use of antibiotic prophylaxis was associated with prolonged pregnancy, reduction in chorioamnionitis (RR 0.66, 95% CI 0.46–0.96), and neonatal infection (RR 0.67, 95% CI 0.52–0.85) [94].

*Respiratory Syncytial Virus (RSV)**Epidemiology*

RSV is the most common cause of lower respiratory tract infections (LRTI) in children worldwide, with 22% of LRTI due to RSV. A systematic epidemiologic review of data estimated 33.8 million RSV-LRTI worldwide in 2005 in children <5 years of age, with 3.4 million requiring hospitalization [95]. LRTI caused by RSV result in an estimated 41,000–199,000 deaths yearly, with >99% of these occurring in low-income countries [96]. High-risk groups for RSV include premature infants, very low birth-weight infants, and HIV-infected or other immunocompromised children [97,98]; however, most children admitted to the hospital with RSV-LRTI were previously healthy [99].

Clinical Presentation

RSV is transmitted through direct or close contact with contaminated secretions and there is a latent period of 4–6 days before clinical symptoms. The first signs in infants include nasal discharge and congestion, cough, fever, and decreased appetite; in up to 30% of infants <2 years, a LRTI develops, varying in severity. As the infection progresses, other symptoms, including tachypnea, wheezing, persistent cough, increased respiratory effort, and feeding difficulties, develop with the typical clinical

picture of bronchiolitis. Although most cases are not severe, a subgroup of children develops acute respiratory failure, requiring ventilator support. RSV results in potential increased risk of longer-term respiratory problems, such as asthma. Nonrespiratory manifestations of RSV have been described, including acute otitis media, central nervous system (CNS), cardiovascular, and liver [100].

Management

Most RSV infections are self-limiting and resolve in up to 21 days after symptom onset. However, if there is respiratory distress or dehydration, IV fluids and supplemental oxygen are needed. Electrolyte imbalance, such as hyponatremia, may be seen in seriously ill infants. Cochrane reviews support the absence of efficacy of systemic corticosteroids and bronchodilators [101,102]. Antibiotics are recommended only if there is evidence of bacterial co-infection. Frequent hand washing and isolation of RSV-infected patients has proven effective in reducing nosocomial RSV infections [103].

Prevention

Palivizumab is a monoclonal antibody that targets the RSV F protein and has been approved by the FDA and European Medicines Agency for immunoprophylaxis in high-risk infants. A Cochrane systematic review of randomized clinical trials comparing palivizumab prophylaxis with placebo found that children at a higher risk of severe RSV infection were less often hospitalized or admitted to intensive care units and had fewer days on oxygen [104]. However, it is expensive and requires monthly IV infusion, which makes it inaccessible to populations with the highest burden of disease. Patent expiration for palivizumab is expected soon and this may be associated with increased opportunities for lower pricing and greater access.

Active pediatric and passive immunizations via maternal vaccination are potential strategies for prevention and several vaccine approaches are in development. Transmission dynamics studied at the community level in Kenya show that transmission mainly occurs through introduction of RSV via siblings in school, supporting the potential effectiveness of vaccinating older siblings to provide indirect immunity in the household [105]. Several antiviral drugs for RSV are also being investigated in clinical trials.

Sexually Transmitted Infections (STIs)

A recent systematic review and meta-analysis of STI prevalence estimates among pregnant women attending antenatal care facilities in sub-Saharan Africa estimated 2.7–3.7% prevalence for gonorrhea (GC), 6.1–6.9% for chlamydia, 17.8–29.1% for trichomoniasis, and 3.5–4.5% for syphilis [106]. In the US National Health and Nutrition Examination Survey (NHANES) from 1999 to 2002, HSV-2 seroprevalence among pregnant women was 22% [107] and globally >250 million women of childbearing age are living with HSV-2 [108]. HSV type 1, which commonly causes orolabial ulcers (cold sores), is thought to be responsible for approximately 50% of incident infections affecting in the genital area, likely facilitated by oral–genital contact [109].

There is a high prevalence of asymptomatic STIs in pregnancy [110], but STIs (even if asymptomatic) are associated with significant adverse obstetrical and perinatal/neonatal outcomes and also increased risk of HIV acquisition or transmission [111].

Gonorrhea, Chlamydia, and Trichomoniasis

Gonorrhea and/or chlamydia are associated with increased risk of preterm birth, premature rupture of membranes, neonatal pneumonia (10–20% of newborns with untreated chlamydial infection in the mother), and neonatal conjunctivitis or ophthalmia neonatorum (50% of newborns with untreated infection in the mother), which can lead to blindness. Trichomoniasis has been associated with preterm birth and LBW [112].

In higher-resource areas, the most sensitive diagnostic tests are NAATs, which can be performed on urine, vaginal, or cervical specimens. Most diagnoses and treatments of these infections in LMIC are based on syndromic management of vaginal discharge, allowing for same day treatment; however, this approach is relatively nonspecific and will not detect asymptomatic infections. There is increasing

prevalence of GC resistance to antibiotics used for standard treatment, resulting in frequently changing guidelines for treatment in high-income countries and increased risk for treatment failure in LMIC. Culture is required for antimicrobial susceptibility testing [111].

Syphilis

Globally, maternal syphilis is the most common infection associated with stillbirth in low-resource settings [113], and untreated syphilis results in congenital syphilis in about 16% of cases; it is associated with 90,000 neonatal deaths and 65,000 infants born prematurely or with LBW. The overall rate of adverse outcomes ranges from 58.4% to 81.8% [114]. Frequency of maternal-to-child transmission is higher later in gestation, but the severity of fetal infections is higher earlier in gestation. Congenital syphilis is associated with long-term sequelae, including deafness, blindness, and neurologic impairment.

The standard diagnosis of syphilis in pregnancy involves serologic testing using a non-treponemal test (e.g., RPR, VDRL) with reactive results confirmed by a treponemal-specific test (e.g., FTA-ABS, TP-PA), although a reverse screening algorithm with primary screening using treponemal tests is being used increasingly [115], which can exclude women with false-positive nontreponemal results. Currently, only about 30% of pregnant women with syphilis in sub-Saharan Africa receive testing and treatment. Accurate, rapid, point-of-care diagnostic tests for syphilis are now available. They are inexpensive, do not need refrigeration or specialized equipment, can be performed on finger-stick specimens, require minimal training, and provide results in 20 min or less [116].

Most of the consequences of maternal syphilis can be prevented if infected mothers are identified before the third trimester of pregnancy and treated with penicillin at least 30 days before delivery [117]. Although the CDC recommends three doses of benzathine penicillin at weekly intervals with late latent syphilis or of unknown duration, [111], some data suggest effectiveness in preventing adverse pregnancy outcomes with only one dose, and this may be more feasible in resource-constrained settings [118].

Herpes Simplex Virus (HSV)

The primary concern of HSV in pregnancy is maternal–fetal transmission at the time of delivery as a result of direct contact with the virus shed from infected sites; shedding can occur without symptoms. The risk of neonatal infection is the highest in women with primary or first-episode nonprimary genital HSV infection near the time of delivery due to higher frequency and concentration of viral shedding. Recurrent infection carries a risk for neonatal infection of only 1–3%, probably related to HSV-specific maternal antibodies and lower concentration and duration of viral shedding [119]. However, given the relative frequency of prevalent HSV, the largest numbers of infected infants are related to viral shedding at the time of delivery. In utero congenital HSV, infection can occur but is rare.

Clinical Presentation

Primary genital HSV is the occurrence of HSV infection in those without preexisting antibodies to either HSV-2 or HSV-1. Clinical presentation can include painful genital ulcers, fever, tender inguinal adenopathy, and, rarely, more severe systemic illness or disseminated infection. However, a study of pregnant women who developed primary HSV found that only one-third had symptoms consistent with genital HSV [120]. The first episode of genital HSV infection may be nonprimary, if there are preexisting HSV antibodies different from the HSV type responsible for the current symptoms. Recurrent genital shedding with or without symptoms occurs episodically and symptoms, if present, are milder than with primary infection. In the presence of clinical findings, HSV infection is diagnosed most commonly with culture or polymerase chain reaction, and in limited resource settings, HSV is included in syndromic management of genital ulcers. Type-specific antibodies can identify HSV infection in women without symptoms.

Management in Pregnancy

Therapy with acyclovir or valacyclovir should always be offered to patients with primary or first-episode genital nonprimary infection, regardless of the gestational age [111]. Treatment may be given for recurrent infection for symptomatic relief. Suppressant antiviral therapy is recommended at 36 weeks of gestation through delivery for women with a history of genital HSV to reduce the risk of viral shedding at the time of delivery and the need for Cesarean delivery (ACOG). Cesarean delivery is recommended by the CDC and ACOG as soon as possible after the onset of labor in women with active genital herpetic lesions or prodromal symptoms [111,121], based on a large prospective study of over 58,000 pregnant women showing a protective effect against fetal transmission [119]. Some experts recommend cesarean delivery for all women who develop a primary HSV infection in late pregnancy, because of more prolonged viral shedding and given the higher risk of neonatal transmission [122].

Neonatal HSV

Neonatal HSV may be classified into three main categories for therapeutic and prognostic considerations: localized skin, eye, and mouth (SEM) lesions (45%); CNS (30%); and disseminated disease (25%). There is a high risk of progression from SEM to CNS or disseminated disease if untreated; eye involvement can lead to permanent vision impairment. Mortality of disseminated disease exceeds by 80 percent if untreated [123].

Diagnosis of neonatal HSV infection is clinically challenging and requires a high index of suspicion with a compatible clinical presentation. Laboratory diagnosis of HSV involves culture, PCR assays, or detection of viral antigens with rapid direct immunofluorescence assays, but negative tests do not exclude neonatal HSV. Lumbar puncture for CSF studies and other laboratory evaluations are recommended. Empiric therapy with acyclovir should be considered in circumstances where HSV is considered a possible diagnosis.

Summary

Infectious diseases are a major contributor to maternal and newborn morbidity and mortality and adverse obstetrical outcomes. Great progress has been made in both treatment and prevention of many infections, but accurate and timely diagnosis and sustainable access to effective interventions are ongoing needs. Country-specific and regional clinical and microbiologic surveillance systems are needed to monitor the burden of disease and evolution of patterns of resistance. With several infections promising vaccines, candidates are being developed and tested.

Practice Points:

- All pregnant and breastfeeding women with HIV should be on ART with lifelong treatment preferred.
- HIV+ pregnant women in TB-endemic areas should be screened at each visit for cough, fever, night sweats, or poor weight gain.
- IPT and use of ITNs are key strategies for prevention of malaria in pregnancy.
- Accurate rapid, point-of-care diagnostic tests for syphilis are now available and should be used to improve access to antenatal screening.
- Broad-spectrum antibiotics should be started promptly with a diagnosis of chorioamnionitis and continued for one-dose postpartum.
- The use of prophylactic antibiotics with C-section has been associated with decreased incidence of maternal infectious morbidity.
- Screening pregnant women for GBS colonization and giving IAP for GBS colonization and other risk factors can help prevent neonatal sepsis.
- Daily application of chlorhexidine to the umbilical cord stump in the first week of life for newborns who are born at home in settings of high-neonatal mortality (30 or more neonatal deaths/1000 live births) has been identified as an effective intervention to reduce neonatal mortality.

Research Agenda:

- more accurate clinical and microbiologic surveillance systems to characterize burden of disease and evolving patterns of resistance
- better understanding of mechanisms of transmission
- validated risk-stratification strategies to improve the predictive ability to detect maternal and neonatal infections
- implementation strategies to ensure access to ART and adherence and retention during and after pregnancy for HIV+ women
- accurate point-of-care tests for infections
- development and testing of promising vaccine candidates and strategies

Conflict of interest

The authors have no conflicts of interest.

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Short cervix detection in pregnant women by transabdominal sonography with post-void technique

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Abstract

Purpose This study aimed to evaluate the diagnostic properties of transabdominal sonography with the post-void technique for cervical length measurement.

Methods This study was a prospective cohort study. The inclusion criteria were pregnant women aged 18–40 years with gestational age of 18–23 completed weeks. Transabdominal sonography with vertical bladder depth of less than 5 cm and transvaginal cervical length measurements were carried out by a single experienced sonographer.

Results There were 307 eligible pregnant women. The mean age of all subjects was 29.0 years. The mean cervical length obtained through transabdominal and transvaginal measurement was 3.33 and 3.47 cm, respectively. Ten patients (3.3 %) were identified as having a short cervix using transvaginal sonography, and 12 patients (3.9 %) were identified using transabdominal sonography.

Conclusion Transabdominal sonography with vertical bladder depth of less than 5 cm performed better compared with transvaginal sonography. It may not be necessary to perform transvaginal sonography if transabdominal sonography reveals the cervical length to be more than 2.5 cm.

Keywords Cervical length · Short cervix · Preterm birth · Screening

Introduction

Preterm birth is a major cause of perinatal morbidity and mortality. A short cervix, defined as a transvaginal measurement of less than 2.5 cm [1], is one contributing factor in preterm birth. Detection and treatment of a short cervix may reduce perinatal morbidity, such as preterm births, neonatal morbidity, or perinatal losses. Treatment options are vaginal progesterone, cervical cerclage, and pessary. These options have comparable perinatal morbidity and mortality.

Transvaginal cervical length measurement is a standard tool to identify a short cervix [2, 3]. This method has some limitations, including the fact that it is time-consuming and inconvenient for both patients and physicians. Transabdominal sonography is a more convenient option for short cervix detection. Diagnostic properties of transabdominal compared with transvaginal sonography are still in debate. The correlation of both methods varies from 0.77 to 0.82 [4, 5], while the sensitivity of transabdominal sonography is 43 % [6]. Transabdominal sonography with the empty bladder technique has been controversial in terms of correlation and difficulty [4, 7]. One report [4] showed that the cervical length as measured by the transvaginal method was no different from that as measured by the transabdominal method with emptied bladder (3.61 vs. 3.57 cm; $P = 0.20$). This study aimed to evaluate the diagnostic properties of transabdominal sonography using the emptied bladder technique for cervical length measurement in Asia, where there are limited data available on this technique.

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Materials and methods

We conducted a prospective study at the Department of Obstetrics and Gynecology, Faculty of Medicine, Khon Kaen University, Thailand. The study period was from February to November 2014. The inclusion criteria were pregnant women aged 18–40 years with gestational age of 18–23 completed weeks. Subjects were excluded if they exhibited any of the following conditions: a history of cervical conization, vaginal bleeding during the current pregnancy, cervical cerclage in situ, or any fetal anomaly detected using ultrasonography. The study protocol was approved by Khon Kaen University Ethics Committee (HE561490). Eligible subjects signed an informed consent form prior to study participation.

Baseline characteristics and histories of preterm birth and abortion were recorded for all of the subjects who participated. Both transabdominal and transvaginal sonography were performed in all patients by a single experienced sonographer who had attended a cervical assessment course organized by the Fetal Medicine Foundation in London, United Kingdom. The ultrasound machine used was a Voluson E8 Expert series (GE Healthcare, Milwaukee, WI, USA) with TA probe RAB 2-5D and TV probe RIC 5-9D. The technique used was that modified from Berghella et al. [3], and performed essentially as had been previously described by Sonek et al. [8].

Each patient emptied her bladder prior to scanning. Fetal anomaly screening and measurement of cervical length was first performed using a transabdominal sonography probe. The bladder vertical depth, which should be less than or equal to 5 cm, was measured and recorded in centimeters to prevent distortion of the cervical canal measurement [9]. The cervix was visualized in the sagittal plane, and care was taken to obtain the full length of the cervical canal. The image was adjusted, so that the cervix occupied at least two-thirds of the screen, and the external os and internal os were clearly visible. The cervical length was measured from the internal os to the external os along the endocervical canal. Two measurements were made and added together where the cervical canal was curved and could not be measured in one plane. The first was from the internal os to the point of curvature in the canal, and the second was from that point to the external os. Fundal or suprapubic pressure should not be applied during the examinations [10].

Measurement of the cervix by transvaginal sonography was then carried out within a few minutes after the transabdominal sonography, while the bladder was still nearly empty. The woman was asked to place a pillow underneath the buttocks to elevate and rotate the pelvis to aid in visualization of the full extent of the cervix. A transvaginal

sonography probe was inserted slowly into the anterior fornix of the vagina until the cervix was clearly visible in the sagittal view with the long axis view of echogenic endocervical mucosa along the length of the canal. The probe was then withdrawn to the point where the image became blurred, and just enough pressure was applied to restore the image to prevent distortion of the cervical canal and obscure any funneling of the internal os. All measurements were taken three times, and the shortest measurement was recorded in centimeters by a research assistant. The data on the ultrasound screen were hidden from the sonographer.

The sample size was calculated using a sensitivity of 80 % and an acceptable margin of error of 0.15 with a prevalence of short cervixes at 9.5 % [11]. STATA version 10 (StataCorp, College Station, TX) and Microsoft Office Excel 2012 (Microsoft, Redmond, Washington) were used for statistical analyses. Results were reported as mean, standard deviation (SD), or percentage. Diagnostic properties were calculated, including sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio.

Results

There were 310 eligible subjects; three women were excluded due to fetal anomalies (fetal congenital pulmonary airway malformation, fetal atrioventricular septal defect, and fetal skeleton dysplasia). In total, 307 pregnant women participated in and completed the study protocol. The mean age of all subjects was 29.0 years (range 18–40). The mean gestation age as measured using sonography was 20.1 weeks (range 18–23.7). Nine subjects (2.9 %) had histories of preterm birth. Demographic data, including occupation, parity, pre-pregnancy BMI, body weight at measurement, and histories of abortion, are shown in Table 1.

The mean cervical length obtained using transabdominal and transvaginal measurement was 3.33 (0.46) and 3.47

Table 1 Demographic data of women

Age (mean, SD)	29.0 (5.7)
Gestational age at measurement (mean, SD)	20.1 (1.3)
Nulliparous, <i>n</i> (%)	179 (58.3 %)
Pre-pregnancy BMI (mean, SD)	21.2 (2.8)
BMI at measurement (mean, SD)	23.0 (3.75)
Body weight at measurement (mean, SD)	57.2 (9.9)
History of preterm, <i>n</i> (%)	9 (2.9 %)
History of abortion, <i>n</i> (%)	52 (16.9 %)

SD standard deviation

(0.49) cm, respectively. The mean difference between the methods was 0.14 cm (95 % CI 0.11–0.16). Ten patients (3.3 %) were identified as having a short cervix using transvaginal sonography, and 12 patients (3.9 %) were identified using transabdominal sonography.

A comparison of the number of subjects shown to have a short cervix using transvaginal measurement and those found using transabdominal sonography is shown in Table 2. The sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio were 100 %, 99.3 %, 142.9, 0, and 0.99, respectively. The 95 % confidence intervals for sensitivity and specificity were 69.2–100 % and 97.6–99.9 %, respectively.

Discussion

The prevalence rate of short cervix in Thai pregnant women is 3.3 %, which is lower than in Western countries [6]. A report from the US showed the prevalence of short cervix in pregnant women to be 9.5 % [6]. That study also reported that transabdominal sonography was not an effective method for detecting short cervix in pregnant women due to it having an underdiagnosis rate of 58 %. Another study from the US suggested that transabdominal sonography could be used to detect a short cervix [12]. Among 703 pregnant women, a short cervix length (<2 cm) as detected by transvaginal measurement correlated with 89.8 % of transabdominal measurements less than 30 mm. Saul et al. [4] also reported a strong correlation between transvaginal and transabdominal sonography for short cervical detection. The Pearson correlation between both techniques was high at 0.824. These differences in diagnostic properties of transabdominal sonography for cervical length may be due to the sonographic technique. The first study was performed using transabdominal sonography with a full bladder [6], while the other two studies used the emptied bladder technique [4, 12].

Table 2 Diagnostic performance of transabdominal measurement with cutoff cervical length ≤ 2.5 cm

Cervical length (cm)	TV		Total
	≤ 2.5	> 2.5	
TA			
≤ 2.5	10	2	12
> 2.5	0	295	295
Total	10	297	307

TV transvaginal measurement

TA transabdominal measurement

The results of this study confirmed that the bladder should be empty or only contain a small amount of urine for cervical length detection using transabdominal sonography in pregnant women [12]. We performed transabdominal sonography with a bladder depth of not more than 5 cm [12]. Residual urine with a bladder depth of less than 5 cm does not affect the cervical measurement when using the transabdominal method [12]. Using this technique, the cervical length was comparable between transabdominal and transvaginal sonography (3.52 vs. 3.61 cm; *P* value 0.23) [12]. All subjects in this study emptied their bladders before their sonographic examinations and emptied their bladders again if bladder vertical depth was more than 5 cm.

Likelihood ratios were used in this study instead of positive and negative predictive values due to the low prevalence rate of short cervix length. Both positive and negative likelihood ratios were extreme. If the positive likelihood ratio was more than 10 (142.9 in this study), it suggested a short cervix if the transabdominal measurement was less than 2.5 cm. If the negative likelihood ratio was less than 0.1 (0 in this study), it indicated a high likelihood of excluding a short cervix if the transabdominal measurement was more than 2.5 cm. Similarly, as previously reported, a short cervix (<2.5 cm) was detected using transvaginal sonography in all subjects with cervical length of less than 3.0 cm as measured by transabdominal sonography. It is important to note that the bladder should be emptied [4].

Even though there was only a single sonographer performing measurements for all patients in this study, the cervical lengths were hidden regardless of the method employed. The results of this study may apply to other Asian countries with limited resources. Health care facilities with no transvaginal sonography equipment may use transabdominal sonography with a vertical bladder depth of less than 5 cm as a screening tool for short cervix length in pregnant women with gestational age of 18–23 6/7 weeks. Note that our data set is limited by a relatively small number of patients with a short cervix (10 of 307).

Conclusion

Transabdominal sonography assessment with vertical bladder depth of less than 5 cm performed well compared with transvaginal sonography for cervical length screening in pregnant women. It may not be necessary to perform a transvaginal sonogram if a transabdominal sonogram reveals that cervical length is more than 2.5 cm.

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Compliance with ethical standards

Ethical statements The study protocol was approved by Khon Kaen University Ethics Committee (HE561490).

Conflict of interest The authors report no potential conflicts of interest.

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RESEARCH ARTICLE

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Attitude towards working in rural area and self-assessment of competencies in last year medical students: A survey of five countries in Asia

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Abstract

Background: Five countries in Asia including Bangladesh, China, India, Thailand and Vietnam formed a network called Asia-Pacific Network for Health Professional Education Reforms (ANHER). This network collectively conducted a survey at the national level and at the institutional level (for medical, nursing and public health education). We also undertook an assessment of final year graduates from these schools on their attitudes, competencies and willingness to work in rural areas.

Methods: Pretested anonymous questionnaire comprised of four sections including demographic data, attitudes towards working in rural area, where to work after graduation and perception about competency of respondents was used. Descriptive and analytical statistics were used for data analyses.

Results: About 60 % of students from Bangladesh and Thailand had positive attitude towards working in rural area, 50 % in both China and India and only 33 % in Vietnam. Students' positive attitudes towards their school in terms of preparing or inspiring them to work in rural areas were low across all five countries. Upon graduation and in the next five years, majority of students wanted to work in public sectors. Interestingly confidence about overall competency was quite low.

Discussion: Positive attitude towards working in rural areas varied significantly across five countries in Asia. Medical schools should improve the preparation and inspiration towards working in rural areas for their students.

Conclusion: Medical schools should put more effort in improving students' attitude towards working in rural areas.

Keywords: Medical student, Attitude, Competencies, Rural areas, Asian countries

Abbreviations: ANHER, Asia-Pacific Network for Health Professional Education Reforms (ANHER); SEAR, South East Asia Region; WHO, World Health Organization; WPR, Western Pacific Region

Background

The Lancet Commission on Health Professionals for the 21st Century was launched on the 100th anniversary of the Flexner Report which proposed a replacement of a science based curriculum by a system-based approach in medical education.[1] This prompted a solid movement

in health education reform in different countries, including five Asian countries, namely Bangladesh, China, India, Thailand and Vietnam which are located in the World Health Organization (WHO) South East Asia Region (SEAR) and Western Pacific Region (WPR). These five countries formed a network called Asia-Pacific Network for Health Professional Education Reforms (ANHER) to reform health professional education. The members collectively developed and adopted a common protocol and tools to survey their national scenario and institutional

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levels of medical, nursing and public health education; assess the attitudes, competencies and willingness among their final year graduates to serve rural health services.. These evidences enabled a platform for national strategies to transform their health professional education systems to be more responsive to population health needs. The global emerging challenges include demographic and epidemiologic transitions, technology-driven health care systems unwarranted fragmentation and overly sub-specialization of care, cultural situation as well as domestic health systems dynamics. In 2010, the WHO addressed that approximately one-half of the world population lived in rural area while less than a quarter of physicians worked in remote and rural area despite adequate absolute number of physicians in some low-income countries.[2] The proportion of rural population of Bangladesh, China, India, Thailand and Vietnam in 2014 were 66, 68, 51, 67 and 46 % respectively. [3] The WHO recommended 22.8 as the density threshold of physicians, nursing and mid-wifery personnels per 10000 population. [4] This indicator in 2014 for Bangladesh, China, India, Thailand and Vietnam were 5.8, 29.7, 24.1, 24.7 and 23.0 respectively. [5] At the time of this survey there were no expected proportion of students in Bangladesh, China and India willing to take up rural practice. All medical graduates in Thailand were expected to serve public work mainly in rural areas for three year. In Vietnam, only 1.5 % of medical graduates were expected to work for the government in rural areas. A more complicated problem is about maldistributed health cadres and domestic as well as international migration.[6] A recent survey of Thai medical, dental and pharmacy new graduates in 2012 showed that the overall attitudes towards working in rural areas were quite positive. [7] Medical students in the capital city of Ethiopia had poor attitude towards working in rural areas and majority of them intended to migrate to work abroad mainly in the US and Europe. [8] A cross sectional survey was conducted among final-year medical students at premier government institutions in South Asia (Bangladesh, India, Nepal) and Sub-Saharan Africa (Ethiopia, Kenya, Malawi, the United Republic of Tanzania and Zambia). The overall intention to pursue a rural career was only 15 % (17 % in South Asia and 13 % in Sub-Saharan Africa). [9] A survey conducted among 169 medical students enrolled in Rural Clinical School Program at University of New South Wales in Australia indicated that only about 30 % of these medical students intended to work in rural or remote areas. [10] Cross sectional survey conducted in 792 first year medical students in Madhya Pradesh Province of India revealed that 91 % of students wished to pursue a specialization and 64 % planned to work in urban areas. [11] Our study was aimed at evaluating medical students' attitudes towards working in rural and remote areas, attitudes towards their school in terms of preparing or

inspiring them to work in rural areas, type of work they want to do upon graduation and the next five years and their confidence in overall competency. We also wanted to explore factors associated with these issues.

Methods

Study design

Descriptive and cross sectional analytical study

Population Last year medical students just before graduation in the year 2012 from medical schools in Bangladesh, China, India, Thailand and Vietnam.

Sampling In Bangladesh, classroom census of all medical students studying in the final year (5th year) of their undergraduate course from 23 medical colleges. These medical colleges were selected purposively considering the proportion of public and private medical colleges from all over the country. In China, stratified random sampling by region and types of institution was conducted to obtain 10 % of all institutions. Furthermore, another three leading institutions were purposely selected for the survey as being suggested by two experts in medical education after they reviewed the sampling cohort. In India, we performed a stratified random sampling by geographical region to obtain 10 medical colleges from each of the four regions. In Thailand it was a census of medical students of all 19 medical schools in 2012. In Vietnam sample size was calculated based on the single proportion estimates and was adjusted to ensure representation and geographical distribution area. Sampling for institution was randomly selected from sampling allocation table. Subjects were selected randomly based on student lists.

Data collection We organized a workshop involving researchers from all five countries in Khon Kaen, Thailand to develop the study questionnaire. We pre-tested the questionnaire in a group of medical students in all five countries and modified the questionnaire accordingly. Countries had the flexibility to carry out minor adaptations in the questionnaires as per the country-situation. The survey questionnaire comprised of four sections. The first section was about demographic data including sex, age, and residential location, occupation of father and mother and mode of admission to medical school. The second part was related to attitudes towards working in rural areas and the extent that their medical school had prepared them to work in rural areas using one to five Likert scale. The answers will be grouped into two categories, 'positive' for any answer with the scale 4 or 5, and 'not positive' if otherwise. The third section asked respondents about where to work upon graduation and in the next five years. The last section

was self-assessment of competencies covering administrative competencies, interprofessional skill, communication skill overall clinical skill and overall public health skill. All items were arranged to 1 (not confident at all to 5 (very confident) Likert scale. Mean score at 4 or above will be considered 'confident', while score below 4 will be justified as 'not confident'. The pretested questionnaires were distributed to all randomly selected participants. The questionnaire was anonymous and measured respondent's attitudes subjectively.

Data analysis

The analysis procedure constitutes three parts. Firstly, descriptive statistics were used on demographic data. Demographic information was described in 'percentage' and 'mean'. Secondly, univariate analyses were performed by cross tabulation between each demographic attribute with each dependent variable (rural attitude in section 2, intention to work in section 3, and competency in section 4). Multivariate analysis was conducted using independent variables which yielded statistically-significant results in the descriptive analysis were included in a multilevel fixed effect logistic regression. Country was deemed as cluster (higher level variable). Therefore, the association was already adjusted for cluster effect.

Results

Descriptive statistics

There were altogether 7945 respondents, 1422, 3045, 1978, 1238 and 262 from Bangladesh, China, India, Thailand and Vietnam respectively. The proportions of female students were more than male in all countries except India ranging from 60 % in China to 48 % in India. Mean age ranged from 22.7 years in Bangladesh to 24.9 years in Thailand. A majority of the students in Bangladesh, India and Thailand spent their childhood period in urban areas, while in China and Vietnam, most respondents were in rural areas, Table 1. During high school period most students in all countries lived in urban or suburban areas, Table 1. Majority of parents in Bangladesh, India and Thailand lived in urban areas

while those of China and Vietnam were in rural areas, Table 1. Fathers of majority of students in China and Vietnam were non-professional, 70 % of the fathers in Bangladesh were professional, while it was quite balanced in India and Thailand, Table 2. 70 to 80 % of students' mothers in Bangladesh, China, India and Vietnam were non-professional; the corresponding figure in Thailand was almost 60 %, Table 2. Concerning fathers' education, majority (67 to 79 %) of students' fathers from Bangladesh, India and Thailand completed bachelor degree or higher, the figures in China and Vietnam were 31 and 47 % respectively, Table 2. In general, mothers' education was lower than fathers' education except in Thailand where their levels of educations were similar, Table 2. 61.2, 95.6, 70.2, 36.0 and 85.9 % of students in Bangladesh, China, India, Thailand and Vietnam respectively were admitted through national entrance examination.

About 60 % of students from Bangladesh and Thailand had positive attitude towards working in rural area. The corresponding figures were 50 % in both China and India. Interestingly only 33 % of students in Vietnam had positive attitudes, Table 3. Students' positive attitudes towards their school in terms of preparing or inspiring them to work in rural areas were quite low across all five countries, ranging from 22 % in Vietnam to 46 % in China, Table 3. Interestingly the positive attitude about overall competency was quite low ranging from 25 % in India to 43 % in Bangladesh, Table 3.

Regarding immediate job upon graduation, majority of students wanted to work in public sectors ranging from 57 % in China to 92 % in Thailand, Table 4. Pro-public job preference in the next five years range from 60 % in India to 86 % in Thailand, Table 4.

Inferential statistics

We observed the following by undertaking univariate analyses. Factors associated with attitude towards working in rural area include gender, residence during childhood and high school, parents' residence, professions of father and mother, father's and mother's education and mode of admission into medical schools, Table 5. Factors

Table 1 Residence during childhood and high school and residence of parents

Country	Residence during childhood			Residence during high school			Residence of parents		
	Rural No (%)	Semi-urban No (%)	Urban No (%)	Rural No (%)	Semi-urban No (%)	Urban No (%)	Rural No (%)	Semi-urban No (%)	Urban No (%)
Bangladesh	219 (15.8)	184 (13.3)	981 (70.9)	143 (10.3)	211 (15.2)	1,033 (74.5)	201 (14.4)	151 (10.9)	1,041 (74.7)
China	1,485 (50)	753 (25.3)	733 (24.7)	313 (10.5)	1,756 (59.1)	901 (30.4)	1,297 (43.9)	813 (27.5)	845 (28.6)
India	316 (16.0)	553 (27.9)	1,109 (56.1)	170 (8.6)	537 (27.1)	1,271 (64.3)	277 (14.0)	403 (20.4)	1,298 (65.6)
Thailand	228 (20.3)	183 (16.3)	713 (63.4)	53 (4.7)	110 (9.8)	959 (85.5)	236 (19.7)	214 (17.9)	746 (62.4)
Vietnam	137 (52.3)	54 (20.6)	71 (27.1)	66 (25.3)	95 (36.4)	100 (38.3)	129 (49.2)	48 (18.3)	85 (32.5)
Total	2,385 (30.9)	1,727 (22.4)	3,607 (46.7)	745 (9.7)	2,709 (35.1)	4,264 (55.2)	2,140 (27.5)	1,629 (20.9)	4,015 (51.6)

Table 2 Fathers' and Mothers' occupation and education

Country	Occupation				Education			
	Father		Mother		Father		Mother	
	P No (%)	NP No (%)	P No (%)	NP No (%)	>Bachelor degree No (%)	<Bachelor degree No (%)	>Bachelor degree No (%)	<Bachelor degree No (%)
Bangladesh	1,000 (70.3)	422 (29.7)	340 (23.9)	1,082 (76.1)	1062 (74.8)	357 (25.2)	662 (46.8)	753 (53.2)
China	666 (22.7)	2,268 (77.3)	578 (19.8)	2,336 (70.2)	936 (31.2)	2,059 (68.8)	694 (23.4)	2274 (76.6)
India	1,015 (51.3)	963 (48.7)	425 (21.5)	1,553 (78.5)	1,554 (78.6)	424 (21.4)	1,179 (59.7)	798 (40.3)
Thailand	556 (48.6)	587 (51.4)	492 (42.8)	658 (57.2)	795 (67.0)	392 (33.0)	773 (64.3)	430 (35.7)
Vietnam	101 (38.6)	161 (61.4)	77 (29.7)	182 (70.3)	116 (46.8)	132 (52.2)	93 (36.9)	159 (63.1)
Total	3,338 (43.1)	4,401 (56.9)	1,912 (24.8)	5,811 (75.2)	4,463 (57.0)	3,364 (43.0)	3,402 (43.5)	4,414 (56.5)

P Professional, NP Non Professional

associated with positive attitudes towards their school in terms of preparing or inspiring them to work in rural areas includes parents' residence and mode of admission into medical schools, Table 5. Factors associated with intention to work in public sector upon graduation includes age, residence during childhood and high school, parents' residence, professions of father and mother, father's and mother's education and mode of admission into medical schools, Table 6. Factors associated with intention to work in public sector five years after graduation include age, residence during childhood, parents' residence, professions of father and mother, father's education and mode of admission into medical schools, Table 6. Factors associated with attitude about overall competency include gender, residence during childhood and high school, parents' residence, professions of father, fathers' and mothers' education and mode of admission into medical schools, Table 7.

After adjusted for potential confounding factors and cluster effect using multilevel fixed effect logistic regression the following findings were observed. Factors significantly associated with attitude towards working in rural area include gender, residence during high school and parents' residence. Female students were more likely to have positive attitude than male students. Students

who lived in semi-urban areas during their high school period had significantly lower positive attitude compared to those living in rural areas. Students whose parents lived in semi-urban areas had significantly higher positive attitude compared to those living in rural areas. The only factor significantly associated with positive attitudes towards their school in terms of preparing or inspiring them to work in rural areas is parents' residence. Students with parents living in semi-urban areas had significantly higher positive attitude compared to those living in rural areas. Factors significantly associated with intention to work in public sector upon graduation include residence during childhood and high school and mode of admission into medical schools. Students living in semi-urban areas during their childhood period had significantly more intention to work for public sector while students living in semi-urban areas during high school had less intention to work for public sector. Students admitted by national entrance examination had significantly more intention to work for public sector. Factors significantly associated with intention to work in public sector five years after graduation includes residence during childhood and mode of admission into medical schools. Students living in urban areas during their childhood period had significantly less intention to

Table 3 Attitude towards working in rural areas, attitude towards school in preparing or inspiring to work in rural areas and attitude about overall competency

Country	Attitude					
	towards working in rural areas		towards school in preparing or inspiring to work in rural areas		about overall competency	
	Positive No (%)	Not Positive No (%)	Positive No (%)	Not Positive No (%)	Positive No (%)	Not Positive No (%)
Bangladesh	984 (69.2)	438 (30.8)	647 (45.5)	775 (54.5)	607 (42.7)	815 (57.3)
China	1,425 (46.8)	1,620 (53.2)	1,010 (33.2)	2,035 (66.8)	1,288 (42.3)	1,757 (57.7)
India	1,020 (51.6)	958 (48.4)	640 (32.4)	1,338 (67.6)	505 (25.5)	1,473 (74.5)
Thailand	856 (69.1)	382 (30.9)	530 (42.8)	708 (57.2)	327 (26.4)	911 (73.6)
Vietnam	86 (32.8)	176 (67.2)	58 (22.1)	204 (77.9)	82 (31.3)	180 (68.7)
Total	4,371 (55.0)	3,574 (45)	2,885 (36.3)	5,060 (63.7)	2,809 (35.4)	5,136 (64.6)

Table 4 Upon graduation and next-five year job preference

Country	Job preference			
	Upon graduation		Next-five year	
	Pro Public Sector No (%)	Not Pro Public Sector No (%)	Pro Public Sector No (%)	Not Pro Public Sector No (%)
Bangladesh	944 (71.9)	369 (28.1)	872 (65.6)	457 (34.4)
China	1,678 (57.1)	1,262 (42.9)	2,184 (73.6)	783 (26.4)
India	1,243 (62.8)	735 (37.2)	1,095 (60.0)	731 (40.0)
Thailand	1,098 (92.4)	90 (7.6)	1,029 (85.5)	174 (14.5)
Vietnam	231 (88.2)	31 (11.8 %)	216 (83.1)	44 (16.9)
Total	5,194 (67.6)	2,487 (32.4)	5,396 (71.1)	2,189 (28.9)

work for public sector while students admitted by national entrance examination had significantly more intention to work for public sector. Factors significantly associated with confidence in overall competency include gender and mother's education. Male students and students whose mothers had bachelor degree or higher had significantly higher confidence in overall competency compared to female students and students whose mothers had less than bachelor degree respectively, Table 8.

Discussion

The proportions of female students were more than male in all countries except India. Mean age ranged from 22.7 years in Bangladesh to 24.9 years in Thailand. About 60 % of students from Bangladesh and Thailand had positive attitude towards working in rural area, 50 % in both China and India and only 33 % in Vietnam. Students' positive attitudes towards their school in terms of preparing or inspiring them to work in rural areas were quite low across all five countries. Upon graduation

Table 5 Factors associated with attitude towards working in rural areas and attitude towards school in preparing for working in rural areas (Univariate analyses)

Factors		Positive attitude towards working in rural areas (%)	P-value	Positive attitude towards school in preparing for working in rural areas (%)	P-value
Gender	Female	2459/4432 (55.5 %)	0.000	1590/4342 (36.6 %)	0.252
	Male	1864/3539 (52.7 %)		1252/3539 (35.4 %)	
Residence during childhood	Rural	1189/2385 (49.9 %)	0.000	833/2385 (34.9 %)	0.148
	Semi-urban	923/1727 (53.4 %)		601/1727 (34.8 %)	
	Urban	2118/3607 (58.7 %)		1335/3607 (37.0)	
Residence during high school	Rural	390/745 (52.3 %)	0.000	284/745 (38.1 %)	0.128
	Semi-urban	1,304/2709 (48.1 %)		934/2709 (34.5 %)	
	Urban	2536/4264 (59.5 %)		1544/4264 (36.2 %)	
Parents' residence	Rural	1052/2140 (49.2 %)	0.000	729/2140 (34.1 %)	0.018
	Semi-urban	897/1629 (55.1 %)		628/1629 (38.6 %)	
	Urban	2326/4015 (57.9 %)		1444/4015 (36.0 %)	
Father's occupation	Non Professional	2298/4401 (52.2 %)	0.000	1550/4401 (35.2 %)	0.119
	Professional	1942/3338 (58.2 %)		1233/3338 (36.9 %)	
Mother's occupation	Non Professional	3126/5811 (53.8 %)	0.000	2066/5811 (35.6 %)	0.114
	Professional	1109/1912 (58.0 %)		718/1912 (37.6 %)	
Father's education	< bachelor degree	1726/3364 (51.3 %)	0.000	1202/3364 (35.7 %)	0.678
	≥ bachelor degree	2570/4463 (57.6 %)		1615/4463 (36.2 %)	
Mother's education	< bachelor degree	2347/4414 (53.2 %)	0.001	1563/4414 (35.4 %)	0.256
	≥ bachelor degree	1942/3402 (57.1 %)		1247/3402 (36.7 %)	
National entrance	No	1324/2104 (62.9 %)	0.000	948/2104 (45.1 %)	0.000
	Yes	2015/4796 (42.0 %)		1909/5796 (32.9 %)	

Table 6 Factors associated with intention to work in public sector immediately and five years after graduation (univariate analyses)

Factors		Pro-public at immediately after graduation (%)	P-value	Pro-public at 5 years after graduation (%)	P-value
Gender	Female	2831/4234 (66.9 %)	0.111	2998/4168 (71.9 %)	0.089
	Male	2342/3415 (68.6 %)		2373/3383 (70.1 %)	
Residence during childhood	Rural	1472/2320 (63.4 %)	0.000	1705/2307 (73.9 %)	0.003
	Semi-urban	1158/1688 (68.6 %)		1180/1668 (70.7 %)	
	Urban	2446/3493 (70.0 %)		2391/3427 (69.8 %)	
Residence during high school	Rural	496/740 (67.0 %)	0.138	496/729 (68.0 %)	0.147
	Semi-urban	1650/2647 (62.3 %)		1900/2624 (72.4 %)	
	Urban	2929/4133 (70.9 %)		2873/4055 (70.9 %)	
Parents' residence	Rural	1354/2085 (64.9 %)	0.001	1530/2081 (73.5 %)	0.203
	Semi-urban	1086/1596 (68.0 %)		1132/1579 (71.7 %)	
	Urban	2701/3881 (69.6 %)		2667/3812 (70.0 %)	
Father's occupation	Non Professional	2824/4285 (65.9 %)	0.000	3089/4270 (72.3 %)	0.008
	Professional	2266/3235 (70.0 %)		2197/3161 (69.5 %)	
Maternal occupation	Non Professional	3752/5646 (66.5 %)	0.000	3911/5583 (70.1 %)	0.001
	Professional	1326/1861 (71.3 %)		1358/1828 (74.3 %)	
Father's education	< bachelor	2146/3274 (65.5 %)	0.001	2409/3276 (73.5 %)	0.000
	≥ bachelor	2996/4337 (69.1 %)		1939/3237 (59.9 %)	
Maternal education	< bachelor	2838/4295 (66.1 %)	0.086	3067/4264 (71.9 %)	0.094
	≥ bachelor	2308/3307 (69.8 %)		2271/3237 (70.2 %)	
National entrance	No	1453/1985 (73.2 %)	0.000	1327/1969 (67.4 %)	0.000
	Yes	3726/5671 (65.7 %)		4051/5589 (72.5 %)	

and in the next five years majority of students wanted to work in public sectors. Interestingly confidence about overall competency was quite low.

Factors significantly associated with attitude towards working in rural area include gender, residence during high school and parents' residence. The only factor significantly associated with positive attitudes towards their school in terms of preparing or inspiring them to work in rural areas is parents' residence. Factors significantly associated with intention to work in public sector include residence during childhood and high school and mode of admission into medical schools. Factors significantly associated with confidence in overall competency include gender and mother's education.

Regarding positive attitude towards working in rural or remote area our study revealed a wide variation across five countries. The main reason might be because of very much difference in context between countries. However, majority of students wanted to work in public sectors both upon graduation and five years later. A report from Ethiopia showed that attitude of medical students towards working in rural areas were very poor and the intention to internationally migrate was very high. Only 30 % of these students would like to start practicing medicine in rural areas. [8] A recent survey of

3199 medical and nursing students from Bangladesh, Ethiopia, India, Kenya, Malawi, Nepal, the United Republic of Tanzania and Zambia indicated that only 16 % of these students plan to work in rural areas. [9]

Our study also found that students' positive attitudes towards their school in terms of preparing or inspiring them to work in rural areas as well as confidence about overall competency were quite low across all five countries. Responsible authorities of these medical schools should be informed about this very important issue. In 2010, WHO published a global policy recommendation on "Increasing access to health workers in remote and rural areas through improve retention". Education recommendations included 1) enroll students with rural background, 2) locate health professional schools, campuses and family medicine residency program outside of capitals and other major cities, 3) expose undergraduate students to rural community experience and clinical rotation, 4) revise under and postgraduate curricula to include rural health topics and 5) design continuing education and professional development program that meet the needs of rural health workers and that are accessible from where they live and work. [2] Challenges and lesson learnt in implementing this recommendation in Lao People Democratic Republic and South Africa was

Table 7 Factors associated with attitude about confidence in overall competency (univariate analyses)

Factors		Confidence (%)	P-value
Gender	Female	1388/4342 (32.0 %)	0.000
	Male	1376/3539 (38.9 %)	
Residence during childhood	Rural	894/2385 (37.5 %)	0.003
	Semi-urban	614/1727 (35.6 %)	
	Urban	1199/3607 (33.2 %)	
Residence during high school	Rural	279/745 (37.4 %)	0.000
	Semi-urban	1025/2709 (37.8 %)	
	Urban	1403/4264 (32.9 %)	
Parents' residence	Rural	807/2140 (37.7 %)	0.000
	Semi-urban	605/1629 (37.1 %)	
	Urban	1320/4015 (32.9 %)	
Father's occupation	Non Professional	1608/4401 (36.5 %)	0.003
	Professional	1112/3338 (33.3 %)	
Maternal occupation	Non Professional	2057/5811 (35.4 %)	0.343
	Professional	654/1912 (34.2 %)	
Father's education	< bachelor	1281/3364 (38.1 %)	0.000
	≥ bachelor	1468/4463 (32.9 %)	
Maternal education	< bachelor	1620/4414 (36.7 %)	0.001
	≥ bachelor	1122/3402 (33.0 %)	
National entrance	No	650/2104 (30.9 %)	0.000
	Yes	2127/5796 (36.7 %)	

reported recently. [12] An online survey of 156 last year medical students in the United States concluded that students had performed most basic skills infrequently and had no confidence in performing these skills without assistance, similar to our observation.[13] In addition, self-assessment of clinical competency by graduates in Yemen was found to be overestimated comparing to expert's assessment. [14] Problem-based learning at the institute has an impact upon graduate competency. [15]

Factors associated with attitude towards working in rural area included gender, domicile during high school and parents' domicile and those with intention to work in public sector included domicile during childhood and high school and mode of admission into medical schools. A retrospective cohort study from Nepal reviewed that factors associated working in rural area included paramedical background, rural domicile at birth and poor academic performance. [16] The recent study in India did not find

Table 8 Factors associated with attitude towards working in rural areas, attitude towards school in preparing or inspiring to work in rural areas and attitude, job preference immediately and five years after graduation and overall competency (multivariate analyses)

Attitudes	Factors	Odds ratio (95 % CI)
1. Working in rural areas	Male gender	0.88 (0.86, 0.98)
	High school residence in semi-urban area	0.83 (0.69, 0.99)
	Parents' residence in semi-urban area	1.34 (1.10, 1.62)
2. School in preparing to work in rural area	Parents' residence in semi-urban area	1.18 (1.03, 1.35)
3. Job preference immediately after graduation	Childhood residence in semi-urban area	1.34 (1.10, 1.64)
	High school residence in semi-urban area	0.78 (0.64, 0.95)
	National entrance	1.30 (1.13, 1.49)
4. Job preference five years after graduation	Childhood residence in urban area	0.81 (0.66, 0.99)
	National entrance	1.57 (1.37, 1.80)
5. Overall competency	Male gender	1.39 (1.26, 1.54)
	Mother education (Bachelor degree or higher)	1.19 (1.05, 1.36)

significant association between graduation from public or private medical schools and job preference in the future.[11] In Ethiopia, students with rural background were more likely to intend to work in rural areas compared to those with urban background. [8]

Limitations of the study

This is a multi-country studies involving five major countries in Asia which represent more than one half of world population. Although common protocols were used, contribution varied in different countries from 3.3 to 38.3 %. Furthermore, rural, urbanized and semi-urbanized areas were self-defined country by country which might not be exactly the same. However, this issue is very much context specific and investigators in the country would have clear ideas what rural, sub-urban and urban means in their context. All five countries defined rural area as area that is located outside towns and cities.

Conclusion

Medical students' low positive attitudes towards their school in inspiring them to work in rural area as well as their low confidence in overall competency to work in rural area should strongly alert administrative authorities of medical schools. Appropriate strategies including more emphasis on community and competency-based learning should be implemented based on local context. Medical schools should provide more learning opportunities to improve students' confidence by implementing adequate simulation and early clinical exposure in learning processes e.g. rotation to community hospitals for clinical skills and more engagement in health system.

Additional file

Additional file 1: Student survey. (PDF 132 kb)

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Availability of data and materials

All datasets on which the conclusions of the paper rely are already presented in the main manuscript. An English language copy of the survey used is provided as an Additional file 1.

Authors' contributions

WLC, PL and PVC conceptualize and design the study. All authors involved in data collection, analyses and interpretation. WLC and PL drafted the manuscript. HN, WW, KM and PVC critically revised the manuscript for important intellectual content. All authors approved of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests

The authors declare that they have no competing interest.

Consent for publication

Not applicable

Ethical approval and consent to participate

Ethical approval for the country-specific data collection was obtained from the ethics committee in each participating institute. The name of the ethical approval committee included 'Bangladesh Institute Name: National Institute of Health (NIH) Office of Extramural Research', 'Peking University Institutional Review Board', 'Indian Institute of Public Health-Delhi', 'Institute for The Development of Human Research Protections (IHRP) in Thailand', 'Hanoi School of Public Health Institutional Review Board'. All the selected respondents were given assurance of confidentiality that the information gathered will be used exclusively for research purposes. We introduced survey participants to the purpose, main contents, and benefits by including a paragraph on the first page of the questionnaire. We also indicated that participation in the survey was anonymous and voluntary and filling in the questionnaire meant that the students were willing to participate in the survey.

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Clinical practice patterns on the use of magnesium sulphate for treatment of pre-eclampsia and eclampsia: a multi-country survey

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Objective To characterise the current clinical practice patterns regarding the use of magnesium sulphate (MgSO₄) for eclampsia prevention and treatment in a multi-country network of health facilities and compare with international recommendations.

Design Cross-sectional survey.

Setting A total of 147 health facilities in 15 countries across Africa, Latin America and Asia.

Population Heads of obstetric departments or maternity units.

Methods Anonymous online and paper-based survey conducted in 2015.

Main outcome measures Availability and use of MgSO₄; availability of a formal clinical protocol for MgSO₄ administration; and MgSO₄ dosing regimens for eclampsia prevention and treatment.

Results Magnesium sulphate and a formal protocol for its administration were reported to be always available in 87.4% and 86.4% of all facilities, respectively. MgSO₄ was used for the treatment of mild pre-eclampsia, severe pre-eclampsia and

eclampsia in 24.3%, 93.5% and 96.4% of all facilities, respectively. Regarding the treatment of severe pre-eclampsia, 26.4% and 7.0% of all facilities reported using dosing regimens that were consistent with Zuspan and Pritchard regimens, respectively. Across regions, intramuscular maintenance regimens were more commonly used in the African region (45.7%) than in the Latin American (3.0%) and Asian (22.9%) regions, whereas intravenous maintenance regimens were more often used in the Latin American (94.0%) and Asian (60.0%) regions than in the African region (21.7%). Similar patterns were found for the treatment of eclampsia across regions.

Conclusions The reported clinical use of MgSO₄ for eclampsia prevention and treatment varied widely, and was largely inconsistent with current international recommendations.

Keywords dosing regimen, eclampsia, low- and middle-income settings, magnesium sulphate, pre-eclampsia.

Tweetable abstract MgSO₄ regimens for eclampsia prevention and treatment in many hospitals are inconsistent with international recommendations.

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Introduction

Pre-eclampsia/eclampsia is a multisystem disorder of pregnancy that carries a high risk of maternal and perinatal mortality and morbidity worldwide.^{1,2} It is estimated that approximately 50 000 women die of pre-eclampsia/

eclampsia each year, accounting for over one-tenth of maternal deaths in Asia and Africa, and around one-quarter of maternal deaths in Latin America.^{3–5}

Magnesium sulphate (MgSO₄) is one of the critical interventions required for reducing severe adverse outcomes from pre-eclampsia/eclampsia. It is the drug of choice for

both prevention and treatment of eclampsia; halving the risk of eclampsia in women with pre-eclampsia and is superior to either diazepam or phenytoin.^{6,7} Currently, the World Health Organization (WHO) and other international organisations recommend two MgSO₄ regimens for eclampsia prophylaxis, namely the Pritchard regimen, which is predominantly administered intramuscularly, and the Zuspan regimen, which is administered intravenously.^{6,8,9} Despite global efforts, translating this knowledge into clinical practice has been challenging in many countries, particularly those with the highest burden of adverse outcomes associated with pre-eclampsia/eclampsia.

Several barriers to access to and use of MgSO₄ have been identified at multiple levels of health systems. These include MgSO₄ not being registered or licensed for use for pre-eclampsia/eclampsia, lack of centralised purchasing and distribution mechanisms, lack of evidence-based clinical protocols, insufficient training and shortage of staff to safely deliver MgSO₄ and fear of toxicity.^{10–15} Nonetheless, there is evidence to suggest that limited coverage of MgSO₄ may be related more to local clinical practices than the availability of the medication. For instance, the WHO Multi-Country Survey on Maternal and Newborn Health (WHO MCS) in 2010/11 reported high coverage of MgSO₄ use for eclampsia prevention and treatment in facilities in many low- and middle-income countries; however, it did not appear to be related to lower rates of adverse outcomes due to pre-eclampsia/eclampsia.¹⁶

The main objectives of this study were to characterise the current clinical practices regarding MgSO₄ administration for the treatment of pre-eclampsia and eclampsia by obstetric providers within the WHO MCS network; to determine what MgSO₄ regimens are recommended for use in these facilities and to what extent these regimens are consistent with current international recommendations. Characterisation of clinical practices related to MgSO₄ use will help to inform international efforts to bridge the current evidence-to-practice gap. The study is part of the converging research activities by WHO towards identifying a clinically non-inferior but simpler MgSO₄ regimen for eclampsia prevention and treatment.

Methods

This was a cross-sectional survey conducted in the network of health facilities in the WHO MCS. Methodological details of the WHO MCS have been published elsewhere.^{17,18} In brief, a stratified, multi-stage cluster sampling approach was used to obtain a global sample of countries from Africa, Asia, Latin America and the Middle East. Within each country, the capital city and two other provinces/states (using probability proportional to the population size sampling method) were selected. In the selected

areas, seven health facilities with more than 1000 births per year were randomly selected. If fewer than seven facilities were available, all health facilities in that area were included. In total, this network includes 370 health facilities in 29 countries.

For the present study, we invited all country coordinators of the WHO MCS research network to participate. Co-ordinators of 15 countries (Afghanistan, Argentina, Brazil, Democratic Republic of the Congo, India, Japan, Kenya, Mexico, Niger, Nigeria, Pakistan, Paraguay, Peru, Sri Lanka, Uganda) representing a total of 233 health facilities agreed to participate in the study (see Figure S1). Country coordinators identified and approached heads of obstetric departments or maternity units of facilities that had previously participated in the WHO MCS. They were invited (via telephone or email) to participate in an anonymous questionnaire survey on institutional clinical practices relating to MgSO₄ use for the treatment of pre-eclampsia and eclampsia. Email addresses were then provided by country co-ordinators to the study investigators.

An online survey (see Appendix S1) was created and sent directly to the identified participants by email by the investigators at WHO in October 2015. No identifying information of individual participants or health facilities was collected. The survey lasted 8 weeks and reminders were sent to all invited participants at 2-, 4- and 6-week time-points. In Uganda, a self-administered paper survey was used in some facilities where email addresses of target participants were not available. In total, 215 of the 233 health facilities that were invited to participate in either an online or a paper-based survey could be reached: 200 out of 218 emails were successfully delivered and 15 printed questionnaires were distributed.

The survey included facility characteristics, MgSO₄ availability and potential barriers to its access, availability and distribution of clinical protocols for MgSO₄ use, MgSO₄ dosing regimens for the treatment of pre-eclampsia and eclampsia, institutional capacity to manage MgSO₄ toxicity, and preferences for different options of simplified MgSO₄ regimens. The survey questionnaire was pre-tested in six health facilities outside the study network and revised accordingly. The questionnaire was translated into Spanish, French and Japanese for use in countries where English is not an official language.

Data analyses were mainly descriptive. Cross-tabulation was used to describe health facility characteristics, availability and use of MgSO₄ by geographical regions. The reported MgSO₄ regimens were grouped by the predominant route of administration. Intravenous maintenance regimens and intramuscular maintenance regimens were sub-categorised into 'higher' or 'lower' dose regimens based on comparison of their total dose to the total 24-hour dose of the Zuspan (28 g) or Pritchard regimen (44 g), respectively.

The WHO Human Reproductive Programme Research Project Review Panel reviewed and approved the scientific content of the study. The WHO Research Ethics Review Committee reviewed and approved the study (protocol ID: A65900). Participation was voluntary and an informed consent form was included in the introductory part of the questionnaire. Participants were able to respond to the survey questions only after granting their consent.

Results

A total of 147 out of 215 (68%) participants who received the survey provided responses. The response rates were similar across regions. Table 1 presents the characteristics of health facilities. There were comparatively more respondents from the African region than other regions. Overall, most health facilities were publicly funded facilities, located in urban areas and not exclusively for maternity service provision; half of them were tertiary-care facilities. The characteristics of the facilities were relatively similar in the African and Asian regions with regard to the level of facilities and whether exclusively for maternity service provision; in the Latin American region, the vast majority of facilities were located in urban areas, most facilities were tertiary hospitals and around one-third were exclusively maternity facilities.

Table 1. Characteristics of health facilities by regions, *n* (%)

Total number of health facilities	Africa <i>n</i> = 61	Latin America <i>n</i> = 40	Asia <i>n</i> = 46	Total <i>n</i> = 147
Type of facility				
Public	48 (78.7)	32 (80.0)	33 (71.7)	113 (76.9)
Private	13 (21.3)	8 (20.0)	11 (23.9)	32 (21.8)
Other	0	0	2 (4.4)	2 (1.3)
Location of facility*				
Rural	12 (20.0)	0	4 (8.7)	16 (11.0)
Peri-urban	12 (20.0)	2 (5.0)	8 (17.4)	22 (15.0)
Urban	36 (60.0)	38 (95.0)	34 (73.9)	108 (74.0)
Level of facility**				
Primary	9 (14.8)	1 (2.6)	7 (15.2)	17 (11.6)
Secondary	27 (44.3)	8 (20.5)	12 (26.1)	47 (32.2)
Tertiary	25 (40.9)	30 (76.9)	27 (58.7)	82 (56.2)
Exclusive maternity facility***				
Yes	9 (14.8)	12 (30.0)	6 (13.3)	27 (18.5)
No	52 (85.2)	28 (70.0)	39 (86.7)	119 (81.5)

*Missing data for one health facility in the African region.

**Missing data for one health facility in the Latin American region.

***Missing data for one health facility in the Asian region.

Availability of MgSO₄ and formal protocol for treatment of pre-eclampsia and eclampsia

As shown in Table 2, MgSO₄ was reported to be always available in 87.4% of all health facilities. This was highest in the Latin American region and lowest in the African region. Among health facilities where MgSO₄ was reported not to be always available (*n* = 16), the most common barriers were inadequate supplies (stock-out) (11/16) and high financial cost of MgSO₄ to the facility (10/16) and to women and their families (8/16).

Most respondents reported that their health facilities had a formal protocol for the treatment of pre-eclampsia and eclampsia, and this was most common in the Latin American region, followed by the African and Asian regions (Table 2). In the three regions, the most common approach used to distribute the protocol was through visible posters in obstetric and labour wards. The protocol was also often communicated through staff training in half of the facilities reporting availability of protocols. About one-third of these facilities provided their protocols to health-care providers as printed materials.

Treatment of pre-eclampsia and eclampsia with MgSO₄

Respondents reported that 24.3% of all facilities used MgSO₄ for treatment of mild pre-eclampsia (35.1% in Latin America, 22.7% in Asia and 18.6% in Africa). Over 90% of health facilities in all three regions used MgSO₄ for treatment of severe pre-eclampsia and eclampsia (Table S1). With respect to the diagnosis and management of MgSO₄ toxicity, 27.8% of all facilities reported having the capacity to routinely measure serum magnesium concentration. This was most common in the Latin American region (48.6%), followed by the Asian region (37.5%) and was uncommon in the African region (7.3%). Calcium gluconate was reported to be always available in 71.0% of all facilities. Availability was higher in the Latin American (94.3%) and Asian (87.5%) regions compared with the African region (44.6%).

Table 3 presents the dosing regimens of MgSO₄ used for the treatment of severe pre-eclampsia by geographical regions. In more than half of all facilities, MgSO₄ was administered as a loading dose followed by continuous intravenous maintenance dose, and in one-quarter of facilities the loading dose was followed by intramuscular maintenance dose. In a few facilities, the maintenance dose was reported to be administered either intravenously or intramuscularly (7.0%) or both intravenously and intramuscularly (3.5%). A loading dose alone and maintenance dose alone were reported to be used in 6.1% and 2.6% of facilities, respectively. Overall, about one-quarter of all facilities used dosing regimens that were consistent with the Zuspan regimen and only 7.0% used regimens that were consistent with the Pritchard regimen.

Table 2. Availability of MgSO₄ and a formal (written) protocol for the treatment of pre-eclampsia and eclampsia by regions, *n* (%)

Total number of health facilities	Africa <i>n</i> = 61	Latin America <i>n</i> = 40	Asia <i>n</i> = 46	Total <i>n</i> = 147
MgSO₄ always available*				
Yes	48 (78.7)	36 (94.7)	41 (93.2)	125 (87.4)
No	13 (21.3)	2 (5.3)	3 (6.8)	18 (12.6)
Formal protocol available**				
Yes	51 (83.6)	35 (97.2)	35 (81.4)	121 (86.4)
No	10 (16.4)	1 (2.8)	8 (18.6)	19 (13.6)
Distribution of the protocol***	(<i>n</i> = 51)	(<i>n</i> = 35)	(<i>n</i> = 35)	(<i>n</i> = 121)
Printed and circulated to staff	13 (25.5)	16 (47.1)	10 (28.6)	39 (32.5)
Communicated in staff training	22 (43.1)	21 (61.8)	16 (45.7)	59 (49.2)
Posted visibly in obstetrics and labour wards	41 (80.4)	21 (61.8)	19 (54.3)	81 (67.5)
Available online at the hospital website	1 (2.0)	10 (29.4)	0	11 (9.2)
Others	1 (1.9)	0	0	1 (0.8)

*Missing data for two health facilities in the Latin American region and two in the Asian region.

**Missing data for four health facilities in the Latin American region and three in the Asian region.

***In health facilities having a clinical protocol for pre-eclampsia and eclampsia treatment, the method of protocol distribution was asked using a multiple choice question. Missing data for one health facility in the Latin American region.

Table 3. Magnesium sulphate regimens used for treatment of severe pre-eclampsia by regions, *n* (%)

Total number of health facilities*	Africa <i>n</i> = 52	Latin America <i>n</i> = 36	Asia <i>n</i> = 42	Total <i>n</i> = 130
Loading dose alone	6 (13.0)	0	1 (2.9)	7 (6.1)
Loading dose + IV maintenance	10 (21.7)	31 (94.0)	21 (60.0)	62 (54.4)
Zuspan regimen	4 (8.7)	10 (30.3)	16 (45.7)	30 (26.4)
Lower dose regimen (with respect to Zuspan regimen)**	2 (4.3)	3 (9.2)	2 (5.7)	7 (6.1)
Higher dose regimen (with respect to Zuspan regimen)***	4 (8.7)	18 (54.5)	3 (8.6)	25 (21.9)
Loading dose + IM maintenance	21 (45.7)	1 (3.0)	8 (22.9)	30 (26.3)
Pritchard regimen	6 (13.1)	1 (3.0)	1 (2.9)	8 (7.0)
Lower dose regimen (with respect to Pritchard regimen)****	15 (32.6)	0	7 (20.0)	22 (19.3)
Higher dose regimen (with respect to Pritchard regimen)*****	0	0	0	0
Loading dose + IV or IM maintenance	6 (13.0)	1 (3.0)	1 (2.9)	8 (7.0)
Loading dose + IV and IM maintenance	2 (4.4)	0	2 (5.7)	4 (3.5)
Maintenance dose alone	1 (2.2)	0	2 (5.7)	3 (2.6)

IM, intramuscular injection; IV, intravenous infusion.

*Missing data for six health facilities in the African region, three facilities in the Latin American region and seven facilities in the Asian region.

**Total dose <28 g given between 1 and 10 hours.

***Total dose >28 g given between 8 and 48 hours.

****Total dose <44 g given between 1 and 24 hours.

*****Total dose >44 g in 24 hours.

Across regions, intravenous MgSO₄ maintenance regimens were used most commonly in the Latin American region (94.0%), followed by the Asian region (60.0%) and less commonly in the African region (21.7%). Of these, 45.7% of health facilities in the Asian region used dosing regimens that were consistent with the Zuspan regimen, whereas 54.5% of health facilities in the Latin American region used higher dosing regimens (compared with the Zuspan regimen). Intramuscular MgSO₄ maintenance

regimens were most commonly used in the African region (45.7%), followed by Asian region (22.9%) and was used rarely in the Latin American region (3.0%). Of these, 32.6% of health facilities in the African region and 20.0% of facilities in the Asian region used lower dosing regimens (compared with the Pritchard regimen) (Table 3).

Similar patterns were found for the treatment of eclampsia across regions (Table 4). Likewise, only 23.1% of all health facilities used dosing regimens that were consistent

Table 4. Magnesium sulphate regimens used for treatment of eclampsia by regions, *n* (%)

Total number of health facilities*	Africa <i>n</i> = 55	Latin America <i>n</i> = 36	Asia <i>n</i> = 42	Total <i>n</i> = 133
Loading dose only	3 (6.1)	0	0	3 (2.6)
Loading dose + IV maintenance	13 (26.5)	31 (91.2)	24 (70.6)	68 (58.1)
Zuspan regimen	5 (10.2)	6 (17.7)	16 (47.1)	27 (23.1)
Lower dose regimen (with respect to Zuspan regimen)**	3 (6.1)	4 (11.7)	2 (5.9)	9 (7.7)
Higher dose regimen (with respect to Zuspan regimen)***	5 (10.2)	21 (61.8)	6 (17.6)	32 (27.3)
Loading dose + IM maintenance	22 (45.0)	2 (5.9)	4 (11.8)	28 (23.9)
Pritchard regimen	9 (18.4)	2 (5.9)	0	11 (9.4)
Lower dose regimen (with respect to Pritchard regimen)****	13 (26.6)	0	4 (11.8)	17 (14.5)
Higher dose regimen (with respect to Pritchard regimen)*****	0	0	0	0
Loading dose + IV or IM maintenance	8 (16.4)	1 (2.9)	1 (2.9)	10 (8.5)
Loading dose + IV and IM maintenance	2 (4.0)	0	5 (14.7)	7 (6.0)
Maintenance dose only	1 (2.0)	0	0	1 (0.9)

IM, intramuscular injection; IV: intravenous infusion.

*Missing data for six health facilities in the African region, two facilities in the Latin American region and eight facilities in the Asian region.

**Total dose <28 g given between 1 and 24 hours.

***Total dose >28 g given between 8 and 48 hours.

****Total dose <44 g given between 1 and 24 hours.

*****Total dose >44 g in 24 hours.

with the Zuspan regimen and 9.4% used regimens that were consistent with the Pritchard regimen. Across regions, 10.2% of health facilities in the African region, 17.7% in the Latin American region and 47.1% in the Asian region used dosing regimens that were consistent with the Zuspan regimen; and 18.4% of health facilities in the African region and 5.9% in the Latin American region used dosing regimens that were consistent with the Pritchard regimen (Table 4).

In this survey, preferences for a simplified regimen in terms of administration route and dosage quantities were investigated. Around two-thirds of all respondents answered to this question. About half of respondents (49/105) felt that an exclusively intravenous regimen was more likely to increase the coverage of MgSO₄ as an intervention for eclampsia prevention and treatment. This preference was most common in the Latin American region (70.0%, 21/30), followed by the Asian (44.1%, 15/34) and African regions (31.7%, 13/41). In addition, 42.5% of respondents reported that a single, one-off dose of MgSO₄ through an intravenous route was more likely to increase coverage. This preference was most common in the African region (50.0%, 22/44) and less common in the Latin American (34.6%, 9/26) and Asian regions (38.9%, 14/36).

Discussion

Main findings

In our study, respondents reported that MgSO₄ was regularly available in the majority of health facilities surveyed,

although it was less commonly available in the African compared to other regions. In spite of the availability of a clinical protocol for treatment of pre-eclampsia and eclampsia in most facilities, the MgSO₄ dosing regimens in use varied widely and were largely inconsistent with current international recommendations. Overall, around one-fifth of the surveyed health facilities in the African region, one-third of those in the Latin American region and half of those in the Asian region used MgSO₄ regimens for treatment of pre-eclampsia in keeping with current recommendations. This pattern is similar for treatment of eclampsia across the three regions.

Strengths and limitations

This survey was conducted in the existing network of health facilities within the WHO MCS across three continents with a focus on resource-constrained settings. It covered a wide geographical scope and provided an opportunity for participants whose first language was not English to participate. For a predominantly online survey, the response rate was considered reasonable and representative of the target sample. However, there are few limitations to be considered. First, inclusion of the capital city as one of the three otherwise randomly selected geographical areas from each country in the WHO MCS network may bias the results. Moreover, the sampling was restricted to health facilities with at least 1000 deliveries per annum and able to provide caesarean section, which were mainly secondary and tertiary-care facilities. These facilities are likely to be better resourced and might not be representative of

smaller facilities although smaller facilities traditionally do not provide care for women with pre-eclampsia. Therefore, an uneven distribution of participating health facilities across the three regions could bias the interpretation of observed differences in clinical practice. Another limitation is that heads of obstetric departments or maternity units were requested to provide a consensus view of institutional clinical practices related to MgSO_4 and it is uncertain to what extent these views captured variations that sometimes exist among individual providers in health facilities. Lastly, the survey assessed the reported use of MgSO_4 regimens rather than its actual (or observed) use. Nevertheless, the significant variation in the regimens used suggests that reporting bias towards internationally recommended regimens is unlikely.

Interpretation

Magnesium sulphate has been recommended internationally as the first-line drug for treatment of severe pre-eclampsia and eclampsia.^{6–9} This recommendation has been introduced into national policies in many countries as an essential intervention for reduction of maternal mortality,¹⁰ which has to a large extent improved the availability of the drug. In our study, MgSO_4 was regularly available in the vast majority of health facilities, albeit being lower in the facilities in the African region. Barriers to accessing MgSO_4 at facility level included inadequate supplies and perceived high costs to both health facility (e.g. costs of equipment and materials to administer and monitor MgSO_4) and users, which are consistent with findings in other studies.^{12,14,15}

Despite the fact that coverage of MgSO_4 for the prevention and treatment of eclampsia has improved, it has not necessarily translated into recommended clinical practice at different health facility levels. We found that about one-quarter of all facilities were using MgSO_4 for treatment of mild pre-eclampsia, despite a lack of recommendation on such practice. This may be related to the evidence from a systematic review, which indicates that women with non-severe pre-eclampsia can also benefit from MgSO_4 in terms of reduction of eclampsia risk.⁷ However, the number needed to treat of 100 with confidence intervals ranging from 100 to 500 raises questions about cost-effectiveness and unnecessary adverse effects when used in this larger proportion of women with pre-eclampsia.^{7,19,20} With respect to the treatment of severe pre-eclampsia and eclampsia, we found a wide variation in the use of MgSO_4 regimens in terms of administration route and dosage quantities, most of which were not in line with international recommendations. This may reflect inadequate introduction of current international recommendations into local protocols, or may be partly attributed to the complexity of administration of the regimens. Studies in India,

Pakistan and Mexico reported that confusion of intravenous and intramuscular regimens as well as challenges in calculating and preparing the dosage were major constraints to administering MgSO_4 appropriately.^{11,14,21}

In our study, intramuscular regimens were more often used in the African region than in the Asian and Latin American regions, probably reflecting regional differences in the availability of supplies and expertise that are required for administration of the intravenous regimens. Compared with the total dosage of the Pritchard regimen, most of these health facilities administered lower dose regimens, probably due to fear of the toxicity of MgSO_4 and insufficient ability to manage severe adverse effects that could potentially result from MgSO_4 . On the other hand, health facilities in the Asian and Latin American regions were more likely to use intravenous regimens. In the Latin American region, higher dose regimens (compared with the Zuspan regimen) were often used, particularly for the treatment of eclampsia. This may reflect healthcare providers' familiarity with intravenous administration of MgSO_4 and a belief that higher dosage may result in greater clinical efficacy, as previously suggested in some old studies.^{22,23} In the absence of standard dose-exposure studies on minimum effective concentration of MgSO_4 ,^{24,25} this variation in clinical practice is likely to persist for some time due to conflicting views on the optimal dosing regimen to prevent eclamptic seizures. The systematic review of small-scale randomised trials and observational studies on several alternative MgSO_4 regimens in recent years have concluded that there is still insufficient evidence on their benefits to justify their introduction into clinical practice.^{26,27}

Conclusion

The clinical practice patterns on the use of MgSO_4 for eclampsia prevention and treatment varied widely, and were largely inconsistent with the current recommendations. To achieve the desirable maternal and newborn outcomes related to pre-eclampsia and eclampsia, evidence-based practices need to be properly implemented at the facility level. In order to bridge the identified recommendation-to-practice gap, future studies should focus on understanding the underlying reasons for non-adherence to international recommendations to complement the knowledge gained from our study.

Considering the barriers to access and use of currently recommended MgSO_4 regimens, a simplified regimen needs to be further explored through a non-inferiority multi-country trial to derive a clinically efficacious regimen that is applicable at all levels of health system and in a wide variety of socio-economic settings. Such a simplified regimen could potentially minimise the challenges of shortages

of supplies and skilled staff that currently impede a wider implementation of recommended clinical practices.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting Information.

Contribution to authorship

OTO and AMG conceived the study. SL and JPV prepared the study protocol with input from OTO. QL was in charge of overall project coordination and data management. PL, GC and ZQ coordinated data collection in the regions. QL and OTO conducted data analysis. QL prepared the first draft of the manuscript. All authors contributed to interpretation of the results and revised the manuscript for intellectual content. All authors approved the manuscript for publication. This article represents the views of the named authors only, and not the views of their institutions or organisations.

Details of ethics approval

The WHO Research Ethics Review Committee reviewed and approved the study on 4 August 2015 (protocol ID: A65900, version 2).

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Countries participating in the Survey.

Table S1. Treatment of pre-eclampsia and eclampsia with magnesium sulphate by regions.

Appendix S1. A survey of global clinical practice patterns in the use of magnesium sulphate for the treatment of pre-eclampsia and eclampsia. ■

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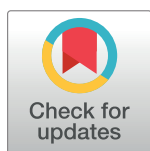
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RESEARCH ARTICLE

The World Health Organization Fetal Growth Charts: A Multinational Longitudinal Study of Ultrasound Biometric Measurements and Estimated Fetal Weight

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Abstract

Background

Perinatal mortality and morbidity continue to be major global health challenges strongly associated with prematurity and reduced fetal growth, an issue of further interest given the mounting evidence that fetal growth in general is linked to degrees of risk of common non-communicable diseases in adulthood. Against this background, WHO made it a high priority to provide the present fetal growth charts for estimated fetal weight (EFW) and common ultrasound biometric measurements intended for worldwide use.

decision to publish, or preparation of the manuscript.

Competing Interests: I have read the journal's policy and the authors of this manuscript have the following competing interests: GP is a WHO statistical consultant and has a contract to give statistical support to the Fetal Growth Study. GP has worked with WHO for 15 years and has a relationship with WHO, both paid (contracts) and unpaid. GP is also a good friend of many of the investigators involved in this study. LDP is a Board Member of the Perinatal Quality Foundation, a nonprofit organization related to the Society for Maternal Fetal Medicine. LDP has received research support from General Electric Medical Systems unrelated to fetal growth. LDP also lectures 1 or 2 times per year at an educational meeting supported by General Electric Medical Systems unrelated to fetal growth.

Abbreviations: AC, abdominal circumference; BMI, body mass index; BPD, biparietal diameter; D. R. Congo, Democratic Republic of the Congo; EFW, estimated fetal weight; FL, femur length; HC, head circumference; HL, humerus length; IQR, interquartile range; LMP, last menstrual period; TI, thermal index.

Methods and Findings

We conducted a multinational prospective observational longitudinal study of fetal growth in low-risk singleton pregnancies of women of high or middle socioeconomic status and without known environmental constraints on fetal growth. Centers in ten countries (Argentina, Brazil, Democratic Republic of the Congo, Denmark, Egypt, France, Germany, India, Norway, and Thailand) recruited participants who had reliable information on last menstrual period and gestational age confirmed by crown–rump length measured at 8–13 wk of gestation. Participants had anthropometric and nutritional assessments and seven scheduled ultrasound examinations during pregnancy. Fifty-two participants withdrew consent, and 1,387 participated in the study.

At study entry, median maternal age was 28 y (interquartile range [IQR] 25–31), median height was 162 cm (IQR 157–168), median weight was 61 kg (IQR 55–68), 58% of the women were nulliparous, and median daily caloric intake was 1,840 cal (IQR 1,487–2,222).

The median pregnancy duration was 39 wk (IQR 38–40) although there were significant differences between countries, the largest difference being 12 d (95% CI 8–16). The median birthweight was 3,300 g (IQR 2,980–3,615). There were differences in birthweight between countries, e.g., India had significantly smaller neonates than the other countries, even after adjusting for gestational age. Thirty-one women had a miscarriage, and three fetuses had intrauterine death.

The 8,203 sets of ultrasound measurements were scrutinized for outliers and leverage points, and those measurements taken at 14 to 40 wk were selected for analysis. A total of 7,924 sets of ultrasound measurements were analyzed by quantile regression to establish longitudinal reference intervals for fetal head circumference, biparietal diameter, humerus length, abdominal circumference, femur length and its ratio with head circumference and with biparietal diameter, and EFW. There was asymmetric distribution of growth of EFW: a slightly wider distribution among the lower percentiles during early weeks shifted to a notably expanded distribution of the higher percentiles in late pregnancy.

Male fetuses were larger than female fetuses as measured by EFW, but the disparity was smaller in the lower quantiles of the distribution (3.5%) and larger in the upper quantiles (4.5%). Maternal age and maternal height were associated with a positive effect on EFW, particularly in the lower tail of the distribution, of the order of 2% to 3% for each additional 10 y of age of the mother and 1% to 2% for each additional 10 cm of height. Maternal weight was associated with a small positive effect on EFW, especially in the higher tail of the distribution, of the order of 1.0% to 1.5% for each additional 10 kg of bodyweight of the mother. Parous women had heavier fetuses than nulliparous women, with the disparity being greater in the lower quantiles of the distribution, of the order of 1% to 1.5%, and diminishing in the upper quantiles. There were also significant differences in growth of EFW between countries. In spite of the multinational nature of the study, sample size is a limiting factor for generalization of the charts.

Conclusions

This study provides WHO fetal growth charts for EFW and common ultrasound biometric measurements, and shows variation between different parts of the world.

Author Summary

Why Was This Study Done?

- Small size at birth is associated with perinatal mortality, child morbidity, and adult health risks, all major global health challenges prioritized by the World Health Organization.
- Ultrasound estimation of fetal weight before birth is today very widely used in clinical practice, and, while essential for the identification and management of high-risk pregnancies, the current reference ranges used worldwide are largely based on single populations from a few high-income countries and are therefore of uncertain general applicability.
- WHO therefore requested new fetal growth charts based on multiple populations to be made available for general use and at the same time provide a foundation for the growing initiative to prevent noncommunicable diseases and promote a healthy life course starting before birth.

What Did the Researchers Do and Find?

- In all, 1,387 healthy women with low-risk pregnancies and unconstrained nutritional and social background from ten countries in Africa, Asia, Europe, and South America were included in a longitudinal study of fetal growth.
- During pregnancy, repeated ultrasound measurements were used to establish international fetal growth charts for head and abdominal circumference, length of the thigh bone, and fetal weight, estimated using a combination of the three measurements.
- Fetal growth showed considerable natural variation, differing significantly between countries. Growth was to a small extent influenced by maternal age, height, weight, and parity, and by fetal sex.
- Similarly, birthweight varied significantly between countries, even after adjustment for differences in the length of pregnancy.

What Do These Findings Mean?

- We suggest that these WHO charts for growth in estimated fetal weight are more suitable for international use than those commonly applied today. However, the differences between countries, with maternal factors, and with fetal sex mean that these growth charts may need to be adjusted for local clinical use to increase their diagnostic and predictive performance.
- The considerable variation in fetal growth and birthweight which occurs even under optimal conditions, and which is not explicable in terms of maternal and population factors, may suggest, first, that such natural variation in offspring size is a collective adaptive strategy that has proved extremely successful from an evolutionary point of view and, second, that major determinants of variation in human development before birth are still to be determined.

- Although the present study encompasses ten countries, it still represents only a small selection when the substantial anthropometric variations existing even within continents are taken into account.

Introduction

Global mortality for infants under age 5 y halved from 90 to 43 deaths per 1,000 live births between 1990 and 2015. This is the result of a tremendous global effort to achieve the UN Millennium Development Goals [1] and the goals of the UN Secretary-General's Every Woman Every Child initiative [2]. Neonatal mortality in the first 28 d declined (by 47%) from 5.0 to 2.6 million deaths annually over this period. Unfortunately, inequality between countries persists, with 98% of neonatal deaths occurring in low- and middle-income countries [3]. Importantly, more than 60% of such deaths are associated with low birthweight due to intrauterine growth restriction or preterm birth or both [4,5]. Ultrasound imaging has become an essential tool for assuring correct gestational age and for fetal size assessment, increasingly so even in societies with restricted resources. Correspondingly, evidence is emerging at the population level that use of ultrasound biometry increases the rate of detection of fetal growth restriction and the identification of those at increased risk of neonatal morbidity [6].

Birthweight, closely linked to fetal growth, is also a marker of risks for noncommunicable diseases in adult life, with cardiovascular diseases, type II diabetes, and obesity being the most prominent [7,8]. While the birthweight gradient across the entire population reflects the distribution of degrees of such risk, it is increasingly evident that it is the developing physiology associated with fetal growth, rather than birthweight per se, that conditions cardiovascular, metabolic, endocrine, and neural functions for the life course, and thus long-term health and disease risks [9]. For this reason, fetal growth data and aspects of intrauterine development need to be included as an important part of an early-life noncommunicable disease prevention initiative, as this targets the time when the effect of an intervention is greatest [10].

A meeting of experts convened by WHO in 2002 reviewed current knowledge on birthweight as a health outcome and identified a need for research to develop fetal growth charts for international use [11]. In 2006, WHO published the multicenter WHO Child Growth Standards [12] using a prescriptive concept that assumes that, under optimal socioeconomic and nutritional conditions, all children follow one growth standard, regardless of ethnic background. Some support for this concept was drawn from previous studies [13,14]. Although widely adopted, the applicability of these child growth standards has been questioned on the grounds of lack of fit to some populations [15,16], especially for the head circumference standards [17].

Recently, a large multicenter study, the Fetal Growth Longitudinal Study of the Intergrowth-21st Project [18], applied the same concept and approach to fetal growth. The study presented growth standards using ultrasound biometric measurements but did not estimate fetal weight (EFW), even though this is the single most widely used clinical assessment of fetal growth today. Another large recent study, the NICHD Fetal Growth Studies, showed significant differences in fetal growth with ethnicity, and established ethnic-specific growth charts [19]. This contradicts the prescriptive concept that one standard fits all. The study was, however, restricted to four self-reported ethnic groups of Asian, Hispanic, black, and white women in the US.

The present study is the fetal component of the WHO Multicentre Growth Reference Study, which aimed to establish growth charts for clinical use based on populations recruited from multiple countries [20].

Methods

Design

This was a multinational observational study approved by the WHO Research Project Review Panel (RP2) and the WHO Research Ethics Review Committee, secondarily approved by the national or local ethics review committee for each study center, and correspondingly carried out according to the Helsinki declaration on ethical principles for medical research in humans [20,21]. All women were recruited specifically for this study, gave written informed consent at inclusion, and otherwise followed their conventional antenatal care program separately from study sessions. Study measurements were revealed to the clinician when the information was thought to be of importance for the management of the pregnancy. The study protocol was published previously [20], so here we present a condensed account of the methods. The study selected participating centers from a range of ethnic and geographical settings, and intended to recruit 1,400 participants. The sample size calculation procedure was published previously [20].

Setting

The following centers participated in the study based on the proficient use of ultrasonography: Centro Rosarino de Estudios Perinatales, Rosario, Argentina; University of Campinas, Campinas, Brazil; University of Kinshasa, Kinshasa, Democratic Republic of the Congo (D. R. Congo); Rigshospitalet, Copenhagen University, Copenhagen, Denmark; Assiut University, Assiut, Egypt; Hôpital Antoine Bécère, Paris, France; University Medical Center, Hamburg-Eppendorf, Germany; All India Institute of Medical Sciences, New Delhi, India; Haukeland University Hospital, Bergen, Norway; and Khon Kaen University, Khon Kaen, Thailand.

Participants

Participants without known health, environmental, and/or socioeconomic constraints were invited to participate in the study. Further inclusion criteria were used: living at an altitude lower than 1,500 m and near the study area (intended to promote compliance for the duration of the study and any possible follow-up studies); age ≥ 18 y and ≤ 40 y; body mass index (BMI) 18–30 kg/m²; singleton pregnancy; gestational age at entry between gestational week 8+0 d and 12+6 d according to reliable information on last menstrual period (LMP) and confirmed by ultrasound measurement of fetal crown–rump length; no history of chronic health problems; no long-term medication (including fertility treatment); no environmental or economic constraints likely to impede fetal growth; not smoking currently or in the previous 6 mo; no history of recurrent miscarriages; no previous preterm delivery (<37 wk) or birthweight $< 2,500$ g; and no evidence in the present pregnancy of congenital disease or fetal anomaly at study entry. Fetal anomalies detected during pregnancy or at birth were noted and verified postnatally. Pregnancies in which small-for-gestation-age fetuses were observed or intrauterine growth restriction was suspected were also noted. All mothers recruited were followed up until the end of the study, apart from those withdrawing consent.

Study Procedures

Women in the first trimester (before week 12+6 d of gestation) attending antenatal care clinics were approached by members of the study team and asked to participate. They were informed about the study objectives and procedures. Those who signed the consent form were enrolled in the study. After the ultrasound scan to assess agreement between gestational age based on

LMP and that based on crown–rump length, they were scheduled for fetal biometry scans at monthly intervals.

All infants had an anthropometric assessment after delivery, including measurement of birthweight. All pregnant women in the study were asked for a 24-h dietary recall at entry into the study (and at 28 and 36 wk of gestation) [22]. Clinically relevant conditions (e.g., hypertension, preeclampsia, and diabetes) occurring during pregnancy and childbirth were noted. Otherwise, no further procedures were added to the routine antenatal care provided at the study centers.

Gestational Age Assessment

Gestational age was confirmed by measuring the crown–rump length between gestational week 8 + 0 d and 12 + 6 d based on LMP and recorded as the average of three measurements. To acquire the crown–rump length, the midline sagittal section of the whole fetus was visualized with the fetus horizontal on the screen at 90 degrees to the angle of insonation. Gestational age was assessed by using the reference charts published by Robinson and Fleming [23]. The woman was eligible for the study provided that gestational age by crown–rump length confirmed LMP-based age within 7 d. The LMP-based age was used for the analyses.

Ultrasound Measurements

The first visit (dating scan) was between 8 + 0 and 12 + 6 wk, and subsequent visits for fetal biometry were scheduled at approximately 4-wk (± 1 wk) intervals at 14, 18, 24, 28, 32, 36, and 40 wk. All scanning appointments were arranged at the time of the dating scan and study enrollment. All participants were scanned in the lateral recumbent position.

The compulsory ultrasound measurements obtained at all visits included the following biometric parameters: biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), femur length (FL), and humerus length (HL). At each examination, all measurements were obtained three times from three separately generated ultrasound images and uploaded electronically (with the associated images) to the data management system. The median of the three measurements of each parameter was used in the analyses.

In addition, a full morphological evaluation (anomaly scan) was conducted at 18–24 wk following standard practice at each center. Fetuses diagnosed with any anomaly were managed according to local clinical guidelines. Their ultrasound measurements were included in the study, and the possible effect on the percentiles derived was evaluated. The following measurement techniques were used. BPD was measured as the outer–inner distance of the parietal bones in a cross-sectional view of the fetal head at the level of the thalami and cavum septi pellucidi or cerebral peduncles. The cerebellum was not included in the section. The measurement was obtained from an image with the midline echo as close as possible to the horizontal plane, 90 degrees to the ultrasound beam. HC was obtained from the same image as BPD as follows: calipers were placed on the outer borders of the occipital and frontal edges of the bone at the point of the midline of the skull, and the ellipse facility was used to follow the outer perimeter of the skull to calculate HC. AC was measured in the transverse section of the fetal abdomen that was as close as possible to circular and that included the stomach and the junction of the umbilical vein and portal sinus. The anteroposterior and transverse diameters were then measured with calipers placed on the outer borders of the body outline. The anteroposterior diameter was measured from the spine to the anterior abdominal wall, and the transverse diameter at a right angle to the anteroposterior diameter. The ellipse facility was used to calculate AC as outlined above. FL was measured from an image of the full femoral shaft in a plane close to 90 degrees to the ultrasound beam. The distal femoral epiphysis was excluded.

Similarly, HL was measured from an image of the full humeral shaft in a plane close to 90 degrees to the ultrasound beam.

The participating centers used identical ultrasound machines during the project (Voluson Expert E8, General Electric, Kretz Ultrasound, Zipf, Austria) equipped with two curvilinear transabdominal transducers (4–8 MHz and 1–5 MHz) and a transvaginal transducer (6–12 MHz), observing that the energy output was set so that thermal index (TI) was <1.0. The TI was automatically recorded and transmitted to the web-based data management system by the ultrasound machine.

Measurement results were stored electronically, with the images together with all information collected from the mother and the perinatal outcomes. EFW was calculated by including HC, AC, and FL in Hadlock et al.'s third formula [24]. To facilitate assessment of relative fetal head size and growth, the ratios FL/HC and FL/BPD were established.

Training and Quality Assurance

The choice of participating centers was based on their proficient use of ultrasound by experienced sonographers. The sonographers participating in the study received specific training for the study and were certified as proficient under the supervision of a qualified instructor, according to a standard protocol. All the ultrasound operators had their scans assessed for quality during their early period in the project. Instruments and techniques used in all centers were standardized, i.e., equipment and training were provided to each of the measurement teams.

Maternal Anthropometric and Nutritional Assessment and Birthweight

Weight wearing light clothing was measured using a beam balance with nondetachable weights and recorded to the nearest 0.1 kg. Height of the mother was measured in the standing position using a stadiometer and recorded to the nearest millimeter. If the reading fell between two values, the lower was recorded.

The 24-h diet recall assessment was carried out by a specifically trained nutritionist or nurse who asked the study participant about food and beverages consumed during the previous 24 h [22]. Further details are available elsewhere [20]. Birthweight was assessed at delivery, and neonatal morphometry carried out within 24 h according to the protocol [20].

Data Management

Data were collected via a web-based data management system developed by Centro Rosarino de Estudios Perinatales, Rosario, Argentina. All data (clinical, anthropometric, nutritional, and fetal biometry measurements plus 2-D/3-D images) were stored in a central server compliant with good clinical practice. Data transmission was encrypted to assure data integrity and patient confidentiality. Access to the web system was password protected, and only authorized users had access. Data changes were documented by a complete audit trail record kept automatically by the web system (recording when, by whom, and why data were changed). Data entered into the web system were checked by the coordinating unit at Centro Rosarino de Estudios Perinatales for completeness, accuracy, reliability, and consistent intended performance. Different kinds of validation procedures were carried out (checking missing values and outliers, cross-checks, cross-time verifications among scanning appointments, and protocol compliance). Measurements and 2-D/3-D images corresponding to fetal biometry had special processing. In collaboration with General Electric Healthcare, Germany, ViewPoint software was installed at all participating centers, allowing a standard interface/procedure for scans and an automatic transfer of fetal biometry measurements/images to the web-based

system. Thus, all fetal biometry measurements considered by the protocol were automatically transferred instead of being entered manually (except for D. R. Congo; there, a complete checking of values was done by the comparison of images and values entered into the web-based system). The above mentioned web-based system and procedures have been used in five previous HRP (UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction)/WHO multicenter studies and are proven to be efficient and compliant with HRP/WHO Standard Operating Procedures as well as with Title 21 CFR Part 11 of the Code of Federal Regulations, which deals with United States Food and Drug Administration guidelines on electronic records.

Adjustments of Analyses Compared with the Protocol and Justifications

Compared with the original protocol [20], the following aspects of the study were adjusted. Reliable information on LMP (confirmed by a measurement of crown–rump length), rather than ultrasound measured crown–rump length alone, was used as the basis for gestational age calculation for the following reasons: there is no evidence that ultrasound dating more accurately determines gestational age than a reliable LMP confirmed by crown–rump length; reliable LMP is the basis for establishing crown–rump length charts for dating; crown–rump length dating translates natural variation of size into variation of gestational age, which is not desirable for a study of growth; and LMP, not crown–rump length, is the accessible, low-cost method for gestational age assessment for all women in the world, and for the low-income areas usually the only one.

The sample size calculation was based on the assumption of normality for the distribution of ultrasound measurements. However, we used quantile regression, which calculates quantiles (i.e., percentiles) directly from the observed measurements without making assumptions about the distribution.

Maternal and fetal conditions occurring during pregnancy were not excluded from the analysis. The rationale for this was that the reference intervals of this study are intended primarily for clinical use and therefore should reflect the population for which they are intended as closely as possible. The pregnancy conditions (e.g., complications) that the study population experienced are those common to low-risk pregnancies around the world. Likewise, excluding all neonates below the 10th percentile of birthweight, as suggested in the protocol [20], would by definition remove the 10% of the participants at the bottom of the range (the vast majority being healthy in this low-risk cohort) and cause a corresponding distortion of the new growth charts, i.e., a substantial upward shift of all the lowest percentiles (10, 5, 2.5, and 1) in the direction of supernormal.

Given the plethora of measurements, we prioritized clinical usefulness in the analyses and results presented here (e.g., EFW and common biometric measurements) and left the following for secondary studies and publications: transverse cerebellar diameter, fetal foot length, 3-D ultrasound acquisitions, maternal anthropometric measurements except height and weight, the second and third sets of dietary 24-h-recall data (at 28 and 36 wk of gestation), and newborn anthropometric measurements except birthweight.

Data Analysis and Statistical Methods

Descriptive statistics were calculated for the women's characteristics at study entry, for mode of delivery, for birth events, and for fetal, neonatal, and maternal conditions, by country and overall. Protocol compliance was evaluated by comparing the dates of the windows of gestational age defined in the protocol with the dates of actual measurements.

The ultrasound measurements were used to estimate reference curves for individual parameters (BPD, HC, AC, FL, HL, FL/HC, FL/BPD) and EFW based on Hadlock et al.'s formula 3 [24]. Reference curves were fitted using quantile regression for reference models, as described by Wei et al. [25] from the work of Koenker [26,27].

The development of reference curves has up to now in general used parametric models, based on assumptions about distribution and on transformation of the observations to normal distributions. Advances brought by computer power and by the work of Koenker and others have made it possible to estimate the distributions directly by estimating their quantiles. Quantile regression is now a well-established technique [26,27], and statistical software is available to fit quantile regression models. Quantile regression fits a function to each chosen quantile using linear programming and has the advantage of not imposing any distributional assumptions. The asymmetry and kurtosis of the fitted distributions may thus assume any form dictated by the data, even changing with gestational age. In addition, quantile regression is more robust against the influence of outliers in the data. The flexibility of the fitting and the fact that any inference drawn is entirely data-driven led us to choose quantile regression as the method for the construction of reference curves.

The estimated quantiles were smoothed by polynomial functions of gestational age. Full models fitted a polynomial on gestational age for each country by including interaction terms between gestational age polynomial and country. Additive terms were included for other covariates.

The models were checked by the residual analysis produced by the software. Hypotheses on the overall importance of covariates were formally tested using likelihood ratio or Wald chi-square tests. In addition, visual inspection of quantile profilers was used to assess the relevance of each covariate in explaining the variation. To compare the distributions of the different countries with the overall distribution, we used quantile–quantile plots. We calculated 95% confidence intervals for the difference between country and global EFW percentiles for particular gestational ages, using the result that the parameter estimates from quantile regression were asymptotically normally distributed [28].

Logarithms of ultrasound parameters and EFW were used for the fitting. This was done only to achieve better numerical accuracy and faster convergence of the fitting algorithm. After the fitting, the results were retransformed to the original scale. To describe growth asymmetry, we used the Bowley coefficient of asymmetry [29], based on differences of semi-quartile ranges relative to the quartile range, for the gestational ages 15 and 40 wk.

Data were analyzed using SAS Software version 9.4 (SAS Institute, Cary, North Carolina, US) and JMP Pro 12 (SAS Institute, Cary, North Carolina, US).

Results

Participants

A total of 1,439 women were enrolled between October 2009 and September 2014, with data collection being completed with the last childbirth in April 2015. Of these, 52 (3.6%) withdrew consent, leaving 1,387 women and their fetuses participating in the study. Table 1 shows the numbers of women recruited, those withdrawing consent, those lost to follow-up, and those having miscarriages or intrauterine deaths, by country. Among women lost to follow-up and with miscarriage or intrauterine death, 10 and 15, respectively, did not contribute ultrasound information. All women other than those withdrawing consent were included in the growth curve analyses if they contributed ultrasound information, with the number in this analysis being 1,362.

Table 1. Number of women recruited to the study by country, with withdrawals and discontinuations.

Country	Number of Women Recruited	Consent Withdrawal		Discontinuation			
				Lost to Follow-Up		Miscarriage/Intrauterine Death*	
		<i>n</i>	Percent	<i>n</i>	Percent	<i>n</i>	Percent
Argentina	143	0	0.0	2	1.4	1	0.7
Brazil	157	4	2.5	2	1.3	3	1.9
D. R. Congo	157	15	9.6	6	3.8	10	6.4
Denmark	142	2	1.4	3	2.1	1	0.7
Egypt	180	25	13.9	11	6.1	9	5.0
France	109	1	0.9	9	8.3	2	1.8
Germany	141	0	0.0	2	1.4	0	0.0
India	146	0	0.0	7	4.8	3	2.1
Norway	140	2	1.4	1	0.7	1	0.7
Thailand	124	3	2.4	3	2.4	4	3.2
Total	1,439	52	3.6	46	3.2	34	2.4

*Two medical abortions, 29 miscarriages, and three intrauterine deaths.

D. R. Congo, Democratic Republic of the Congo.

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Population Characteristics

Statistics for participating women's characteristics, their daily caloric intake, and ethnicity are presented in [Table 2](#). Median age at study entry was 28 y but varied between 24 y (Argentina and Egypt) and 32 y (France). Median maternal height ranged from 155 cm (India) to 169 cm (Germany), and weight from 54 kg (Thailand) to 66 kg (Germany). While overall median BMI was 23.1 kg/m², the median by country ranged from 21.6 kg/m² in Thailand to 25.9 kg/m² in Egypt. Median daily caloric intake in the study group was 1,848 calories according to the 24-h dietary recall assessment, with Thailand having the lowest median, 1,232 calories, and Egypt having the highest median, 2,094 calories. The ethnic distribution of the study group was roughly 20% African (including the peri-Mediterranean Egypt), 20% Asian, and 60% white.

Perinatal Outcomes

[Table 3](#) shows delivery information. The overall rate of spontaneous onset of birth was 67.3%, with a wide range by country: 28.5% in Brazil to 94.5% in D. R. Congo. There was an overall cesarean section rate of 32.1%, with a considerable range from 5.5% in D. R. Congo to 70.1% in Brazil. The occurrence of Apgar score < 7 at 5 min was similar in all countries, i.e., 0%–2.2%. Most of the countries had a similar distribution between female and male neonates except for Egypt, Germany, and Norway, where about 40% of neonates were female. The incidence of preterm birth varied from 3.6% in Germany to 14.7% in Egypt ($p = 0.03$ for differences among countries). It was lowest in D. R. Congo, Denmark, Germany, and Norway and highest in Egypt and India.

Gestational Age at Birth and Birthweight

Gestational age at birth varied between countries from a median of 38 wk 4 d in India to 40 wk 3 d in Norway ($p < 0.001$ for differences among countries) ([Table 3](#)). Norway had the highest median birthweight (3,575 g), and Denmark and Germany had birthweights approximately 100 g less, while Argentina, Brazil, and France had birthweights 200 g less. There is a group

Table 2. Characteristics of the participating women by country at study entry.

Characteristic	Statistic	Argentina (N = 143)	Brazil (N = 153)	D. R. Congo (N = 142)	Denmark (N = 140)	Egypt (N = 155)	France (N = 108)	Germany (N = 141)	India (N = 146)	Norway (N = 138)	Thailand (N = 121)	Total (N = 1,387)
Age (y)	Missing	0	0	0	0	0	0	0	0	0	0	0
	Q1	20	27	24	28	22	28	28	25	26	26	25
	Median	24	30	27	30	24	32	31	27	28	29	28
Weight (kg)	Q3	28	33	31	32.5	28	34	33	30	30	32	31
	Missing	0	0	0	1	8	0	0	0	1	1	11
	Q1	52	57	53	58	57	57	60	50	59	50	55
Height (cm)	Median	58	63	60	62	65	63	66	57	63	54	61
	Q3	64	69	66	67	75	69	72	62	71	59.5	68
	Missing	0	0	0	1	8	0	0	0	1	1	11
BMI (kg/m ²)	Q1	153	160	157	164	155	162	165	152	165	155	157
	Median	157	163	162	168	159	165	169	155	168	157	163
	Q3	162	167	165	171	163	170	174	160	173	161	168
Total calories in 24-h dietary recall	Missing	0	0	0	1	8	0	0	0	1	1	11
	Q1	21.2	21.6	20.8	20.8	23.5	21.1	21.1	20.0	20.5	20.0	21.0
	Median	23.3	23.5	22.9	22.2	25.9	22.9	23.2	23.0	22.2	21.6	23.1
Ethnicity, n (percent)	Q3	26.3	25.8	25.6	24.1	29.0	24.5	24.9	25.3	24.9	23.9	25.4
	Missing	0	0	0	0	4	10	0	28	1	6	49
	Q1	1,666	1,441	1,460	1,584	1,747	1,489	1,674	1,514	1,558	1,004	1,487
Parity (nulliparous n)	Median	1,928	1,709	2,063	1,820	2,094	1,736	1,978	1,831	1,890	1,232	1,848
	Q3	2,189	2,148	2,605	2,053	2,525	2,053	2,285	2,194	2,314	1,534	2,222
	White	143 (100.0)	146 (95.4)	0 (0.0)	140 (100.0)	0 (0.0)	100 (92.6)	136 (96.5)	0 (0.0)	137 (99.3)	0 (0.0)	802 (57.8)
Parity (nulliparous n)	Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.4)	146 (100.0)	1 (0.7)	121 (100.0)	270 (19.5)
	African	0 (0.0)	7 (4.6)	142 (100.0)	0 (0.0)	133 (85.8)	8 (7.4)	3 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	293 (21.1)
	Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	22 (14.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	22 (1.6)
n (percent)	N	137	153	142	139	57	108	141	138	138	121	1,274
	Missing	6	0	0	1	98	0	0	8	0	0	113
	n (percent)	64 (46.7)	108 (70.6)	51 (35.9)	86 (61.9)	21 (36.8)	51 (47.2)	104 (73.8)	115 (83.3)	67 (48.6)	72 (59.5)	739 (58.0)

BMI, body mass index; D. R. Congo, Democratic Republic of the Congo; Q1, first quartile; Q3, third quartile.

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Table 3. Mode of delivery, gestational age at birth and outcomes.

Characteristic	Statistic	Argentina (N = 140)	Brazil (N = 150)	D. R. Congo (N = 127)	Denmark (N = 137)	Egypt (N = 140)	France (N = 97)	Germany (N = 139)	India (N = 139)	Norway (N = 136)	Thailand (N = 114)	All (N = 1,319)
Neonatal sex (n female)	N	140	148	127	136	132	97	139	137	131	112	1,299
Apgar < 7 at 5 min	n (percent)	68 (48.6)	70 (47.3)	67 (52.8)	75 (55.1)	54 (40.9)	45 (46.4)	56 (40.3)	67 (48.9)	52 (39.7)	54 (48.2)	608 (46.8)
	N	140	147	127	135	136	97	139	138	136	113	1,308
Preterm (gestational age < 37 wk)	n (percent)	1 (0.7)	1 (0.7)	1 (0.8)	1 (0.7)	3 (2.2)	0 (0.0)	1 (0.7)	1 (0.7)	2 (1.5)	0 (0.0)	11 (0.8)
	N	140	148	127	137	136	97	139	138	136	114	1,312
Birthweight (g)	n (percent)	12 (8.6)	11 (7.4)	6 (4.7)	8 (5.8)	20 (14.7)	7 (7.2)	5 (3.6)	15 (10.9)	6 (4.4)	9 (7.9)	99 (7.5)
	N	140	148	127	136	117	97	139	137	136	113	1,290
	Q1	2,990	2,910	2,850	3,133	3,000	2,965	3,100	2,656	3,348	2,980	2,980
	Median	3,328	3,290	3,170	3,462	3,100	3,370	3,480	2,975	3,575	3,130	3,300
Gestational age (days)	Q3	3,620	3,608	3,500	3,790	3,500	3,600	3,820	3,200	3,900	3,400	3,615
	N	140	148	127	137	139	97	139	138	136	114	1,315
Mode of delivery, n (percent)	Q1	270	268	270	272	262	273	273	265	276	267	269
	Median	276	273	277	282	271	279	279	270	283	271	276
	Q3	281	278	283	287	280	284	285	277	288	278	282
	Spontaneous	91 (67.9)	41 (28.5)	120 (94.5)	105 (83.3)	64 (45.7)	80 (85.1)	82 (73.2)	84 (64.1)	113 (91.1)	58 (50.9)	838 (67.3)
	Intrapartum CS	30 (22.4)	33 (22.9)	6 (4.7)	7 (5.6)	16 (11.4)	8 (8.5)	24 (21.4)	20 (15.3)	9 (7.3)	26 (22.8)	179 (14.4)
	Elective CS	13 (9.7)	68 (47.2)	1 (0.8)	13 (10.3)	54 (38.6)	6 (6.4)	6 (5.4)	27 (20.6)	2 (1.6)	30 (26.3)	220 (17.7)
	Vacuum	0 (0.0)	0 (0.0)	0 (0.0)	11 (8.7)	0 (0.0)	0 (0.0)	25 (22.3)	5 (3.8)	1 (0.8)	0 (0.0)	42 (3.4)
	Forceps	6 (4.5)	6 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.2)	2 (1.8)	3 (2.3)	11 (8.9)	0 (0.0)	31 (2.5)
	Unknown	0 (0.0)	2 (1.4)	0 (0.0)	1 (0.8)	6 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (0.7)

CS, cesarean section; D. R. Congo, Democratic Republic of the Congo; Q1, first quartile; Q3, third quartile.

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Table 4. Estimated birthweight percentiles for female and male neonates according to completed gestational week.

Percentile	Birthweight (g) by Gestational Age (wk)											
	Female						Male					
	37	38	39	40	41	42	37	38	39	40	41	42
5	1,968	2,315	2,575	2,748	2,835	2,834	2,062	2,451	2,723	2,880	2,921	2,845
25	2,493	2,698	2,891	3,072	3,241	3,398	2,705	2,890	3,061	3,218	3,362	3,491
50	2,786	2,990	3,173	3,336	3,479	3,601	2,919	3,153	3,354	3,519	3,650	3,747
75	2,951	3,217	3,443	3,631	3,779	3,888	3,143	3,387	3,608	3,806	3,982	4,134
90	3,181	3,451	3,682	3,871	4,021	4,130	3,450	3,666	3,871	4,067	4,253	4,428
95	3,238	3,593	3,867	4,060	4,171	4,200	3,584	3,813	4,036	4,251	4,459	4,659

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of countries (D. R. Congo, Egypt, and Thailand) with birthweight a median 400 g less than that of Norway, and lastly India, with birthweight 500 g less. The differences in birthweight between countries were highly significant for all percentiles ($p < 0.001$ for all). When adjusted for gestational age at birth, the differences were still significant for all the percentiles ($p = 0.0018$ for the 5th percentile and $p < 0.001$ for the 10th, 25th, 50th, 75th, 90th, and 95th percentiles). The estimated birthweight according to neonatal sex and gestational age is shown in Table 4.

Maternal Complications and Perinatal Conditions

Conditions occurring in the mother during pregnancy are shown in Table 5, together with fetal malformations and neonatal conditions. In addition to globally experienced maternal complications such as preeclampsia, pregnancy-induced hypertension, gestational diabetes, and anemia, 42 had identified malaria. There was no maternal death. Four small-for-gestational-age fetuses were identified clinically, of which two were examined using Doppler ultrasound; none had abnormal recordings in the umbilical artery or middle cerebral artery, and all were kept in the analysis. It was registered when neonates needed transmission to the neonatal intensive care unit, commonly due to prematurity, respiratory distress syndrome, infections,

Table 5. Maternal complications, fetal malformations, and neonatal conditions by country.

Condition	Argentina (N = 143)	Brazil (N = 153)	D. R. Congo (N = 142)	Denmark (N = 140)	Egypt (N = 155)	France (N = 108)	Germany (N = 141)	India (N = 146)	Norway (N = 138)	Thailand (N = 121)	All (N = 1,387)
Fetal malformation[§]	4 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.9)	1 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)	8 (0.6)
Neonatal condition	19 (13.3)	12 (7.8)	7 (4.9)	10 (7.1)	4 (2.6)	2 (1.9)	9 (6.4)	8 (5.5)	3 (2.2)	9 (7.4)	83 (6.0)
Maternal complication[*]	24 (16.8)	10 (6.5)	42 (29.6)	4 (2.9)	3 (1.9)	8 (7.4)	7 (5.0)	23 (15.8)	6 (4.3)	10 (8.3)	137 (9.9)

Data are given as *n* (percent).

[§]One malformation was discovered at birth, here counted as fetal malformation. Sacrococcygeal cyst (1), Jarcho-Levin syndrome (1), clubfoot (1), polycystic kidneys (1), cardiac malformations (3), cleft palate (1).

^{*}Preeclampsia (22), hypertension (16), gestational diabetes (32), malaria (42), anemia (19), and other (16); some participants had more than one diagnosis.

D. R. Congo, Democratic Republic of the Congo.

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or jaundice. There were three intrauterine deaths and three neonatal deaths, representing a perinatal mortality of 0.4%.

Compliance with Ultrasound Scans

The median number of ultrasound scans (excluding the study entry screening scan) in all women was 6 (range 0–7). Compliance by gestational age window as defined in the protocol is presented in [S1 Table](#), by country and for all countries combined (“Total”). Compliance for all countries combined in each gestational age window was between 89.1% and 100%; 72% of the participants had a complete set of all the scheduled scans. In addition, for each of the measurements BPD, HC, AC, FL, and HL, scans were obtained ≥ 2 times for at least 95% of participants.

Thermal Index

Of the 8,372 scan sessions in the project, 115 had no scans stored and 54 belonged to women who withdrew consent, leaving 8,203 for the statistics. The median TI was 0.2, and none had $TI \geq 1.0$.

Reference Intervals for Biometric Parameters and Estimated Fetal Weight

[Fig 1](#) presents the overall growth curves for BPD, HC, AC, FL, HL, and EFW, and for the ratios FL/HC and FL/BPD, based on quantile regression. The corresponding reference values are shown in [Tables 6–13](#) and in csv format in [S1 File](#).

The distribution of EFW starts with a slight asymmetry to the left (i.e., lower percentiles) in early pregnancy and ends with a very noticeable right asymmetry (i.e., higher percentiles) in later pregnancy. The Bowley coefficient of asymmetry [29], based on differences of semi-quartile ranges relative to the quartile range, was -0.016 for gestational age 15 wk and $+0.111$ for 40 wk.

Influence of Covariates on Growth Percentiles

Fetal sex. Male fetuses were larger than female fetuses as measured by EFW, but the disparity was smaller in the lower quantiles of the distribution (3.5%) and larger in the upper quantiles (4.5%) ([Fig 2](#) and [S2 Table](#), without adjustment for country differences). This difference in size by fetal sex was significant at the 5% level for all percentiles. EFW reference values were also established for female and male fetuses separately ([Tables 14](#) and [15](#)) to allow assessment customized according to fetal sex. For example, at gestational week 37, the median EFW of female fetuses is 84 g lower than that of male fetuses.

Country. Countries differed in EFW ([Fig 3](#)). Using country as a covariate in a quantile regression model, including interaction terms with gestational age, showed significance at the 5% level for all percentiles 5th, 10th, 25th, 50th, 75th, 90th, and 95th ([S2](#) and [S3 Tables](#)). This variation due to country was adjusted for maternal characteristics (mother’s age, parity, height, and weight, or with BMI substituting the latter two) and sex of the fetus. To assess the relative contribution of these variables to the variation in EFW, the Wald chi-square statistics in [S2](#) and [S3 Tables](#) are informative, e.g., for the 5th percentile (quantile 0.05, first table in [S2 Table](#)), as expected, most of the variation (Wald chi-square = 1,797, 1 df) is due to gestational age (linear) as the fetus grows, and there is significant curvature (Wald chi-square = 207, 1 df). Country variation gives Wald chi-square = 36 (9 df); sex of the fetus, 29 (1 df); mother’s height, 26 (1 df); and mother’s age, 22 (1 df), while the Wald chi-square value for weight is negligible. In

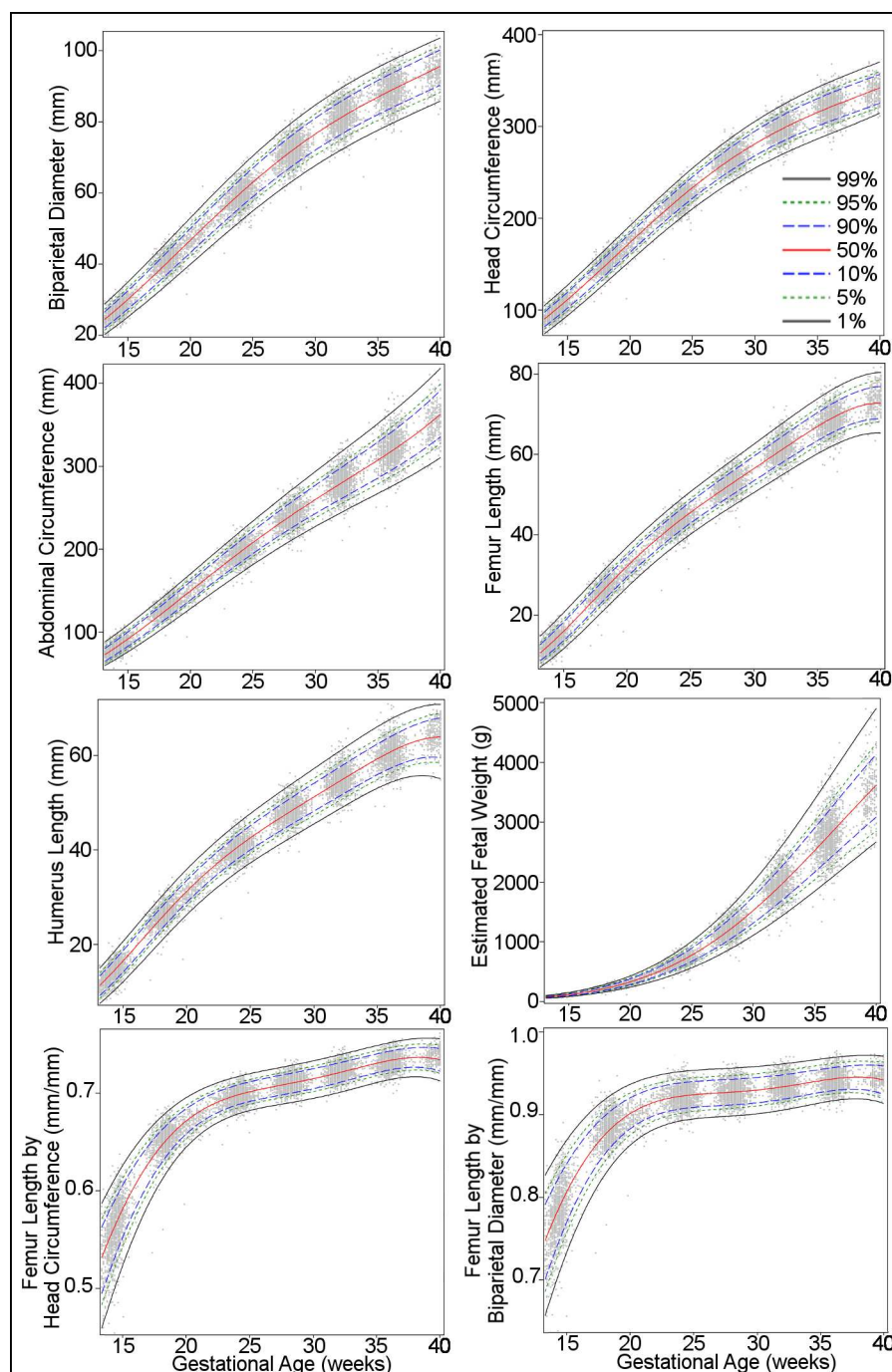


Fig 1. Percentiles for biparietal (outer–inner) diameter, head circumference, abdominal circumference, femur length, humerus length, estimated fetal weight, femur length/head circumference ratio, and femur length/biparietal diameter ratio during gestational weeks 14–40. The percentiles (percent) 1st, 5th, 10th, 50th, 90th, 95th, and 99th (smoothed lines) are based on quantile regression and are shown with the observed values (grey dots).

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the same table, the level of significance is listed for these variables, e.g., $p < 0.001$ for country, highly significant. It is clear that variation due to country also occurs independently of

Table 6. Growth chart for fetal outer–inner biparietal diameter.

Gestational Age (Weeks)	Biparietal Diameter (mm) by Percentile								
	2.5	5	10	25	50	75	90	95	97.5
14	23	24	24	26	27	28	29	30	31
15	26	27	27	29	30	31	32	33	34
16	29	30	30	32	33	35	36	37	38
17	32	33	33	35	36	38	39	40	41
18	35	36	37	38	40	41	43	44	45
19	38	39	40	42	43	45	46	47	48
20	41	42	43	45	47	48	50	51	52
21	44	45	46	48	50	52	53	54	55
22	47	48	50	51	53	55	57	58	59
23	50	52	53	55	57	59	60	61	62
24	53	55	56	58	60	62	64	65	66
25	56	58	59	61	63	65	67	68	69
26	59	60	62	64	66	68	70	71	72
27	62	63	65	67	69	71	73	74	75
28	64	66	67	69	72	74	76	77	78
29	67	68	70	72	74	76	78	80	81
30	69	71	72	74	77	79	81	82	83
31	71	73	74	76	79	81	83	85	86
32	73	75	76	79	81	83	86	87	88
33	75	77	78	81	83	86	88	89	90
34	77	79	80	83	85	88	90	91	92
35	79	80	82	84	87	89	92	93	94
36	80	82	84	86	89	91	93	95	96
37	82	84	85	88	90	93	95	96	97
38	84	85	87	90	92	95	97	98	99
39	85	87	89	92	94	96	99	100	101
40	87	88	90	93	96	98	100	101	102

doi:10.1371/journal.pmed.1002220.t006

maternal characteristics and the sex of the fetus. [Fig 3](#) offers a visualization of country variation for the 10th, 50th, and 90th percentiles for EFW. Country variation in the other ultrasound parameters for the 10th, 50th, and 90th percentiles is presented in [S2–S6 Figs](#). Country differences in EFW percentiles and overall EFW percentiles are presented in [S4 Table](#).

The clinical relevance of the differences between the country quantiles and the global quantiles can be assessed in quantile–quantile plots ([Fig 4](#)). These plots are intended to enable the reader to derive the magnitude of difference in grams for any size and country and percentile. For example, consider the quantile–quantile plot for the individual country 0.05 quantile (i.e., the 5th percentile) for EFW versus the global 0.05 quantile: the 5th percentiles at low values of EFW cannot be differentiated because of the relative smallness of EFW at early pregnancy ([Fig 4](#)). However, at the end of gestation (high values of EFW), the 5th percentile for Norway is 3,200 g, while the overall 5th percentile is 2,800 g; for France it is 2,800 g, and for Egypt, 2,700 g. Similarly, it can be seen that while the 10th percentile for EFW at the end of gestation for Norway is 3,400 g, it is 2,700 g for India (versus about 3,100 g for the global 10th percentile), showing that a fetus weighing 3,200 g would be below the 10th percentile for Norway but well above it for India. The magnitude of the differences among countries can also be appreciated

Table 7. Growth chart for fetal head circumference.

Gestational Age (Weeks)	Head Circumference (mm) by Percentile								
	2.5	5	10	25	50	75	90	95	97.5
14	86	88	91	95	100	104	107	110	112
15	97	99	102	106	111	115	119	122	124
16	108	111	114	118	123	128	132	134	137
17	120	123	126	130	135	140	144	147	149
18	132	135	138	143	148	153	157	160	162
19	145	147	150	155	161	166	170	173	175
20	157	159	163	168	173	179	183	186	188
21	169	172	175	180	186	191	196	199	201
22	181	184	187	193	198	204	209	212	214
23	193	196	199	205	210	216	221	224	227
24	204	207	211	216	222	228	233	236	239
25	215	218	222	227	233	239	245	248	251
26	225	228	232	238	244	250	256	259	262
27	234	238	242	248	254	261	267	270	273
28	243	247	251	257	264	270	277	280	283
29	251	256	260	266	273	280	286	290	293
30	259	264	268	274	281	288	295	299	302
31	266	271	275	282	289	296	303	307	311
32	273	278	282	289	296	304	311	315	318
33	279	284	289	295	303	311	318	322	326
34	285	290	295	302	309	317	324	328	332
35	291	296	300	307	315	323	330	335	338
36	296	301	306	313	321	329	336	340	344
37	302	306	311	318	326	334	341	345	349
38	307	311	315	324	332	339	347	350	354
39	313	316	320	329	337	344	352	355	359
40	319	321	325	334	342	350	357	360	363

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in Fig 5, where selected country percentiles are shown with the corresponding global percentile curve.

Maternal age and maternal height. Maternal age and height seem to be associated with a positive effect on EFW, especially in the lower tail of the distribution, significant at the 5% level, of the order of 2% to 3% for each additional 10 y of age of the mother and 1% to 2% for each additional 10 cm of height (S1D and S1F Fig, without adjusting for country differences).

Maternal weight. Maternal weight seems to be associated with a small positive effect on EFW, especially in the higher tail of the distribution, significant at the 5% level, of the order of 1% to 1.5% for each additional 10 kg of weight of the mother (S1E Fig, without adjusting for country differences).

Parity (0 versus ≥ 1). Parous women had heavier fetuses than nulliparous women, with the disparity being much higher in the lower quantiles of the distribution, of the order of 1% to 3%, significant at the 5% level, and subsiding in the upper quantiles (S1C Fig, without adjusting for country differences).

Table 8. Growth chart for fetal abdominal circumference.

Gestational Age (Weeks)	Abdominal Circumference (mm) by Percentile								
	2.5	5	10	25	50	75	90	95	97.5
14	69	71	73	77	81	86	89	92	95
15	79	81	83	87	92	96	100	103	106
16	89	91	93	98	103	108	112	115	118
17	99	102	104	109	114	119	124	127	130
18	110	113	116	121	126	131	136	139	142
19	121	124	127	132	138	143	148	152	155
20	132	136	139	144	150	155	161	164	167
21	143	147	150	156	162	168	173	177	180
22	154	159	162	167	173	180	186	189	193
23	165	170	173	179	185	192	198	202	205
24	176	181	184	190	197	203	210	214	217
25	186	191	195	201	208	215	222	226	229
26	196	201	205	212	219	226	233	238	241
27	206	211	215	222	230	237	245	249	253
28	215	220	225	232	240	248	256	260	264
29	224	229	234	242	250	258	266	271	276
30	233	238	243	251	260	269	277	282	287
31	241	246	252	260	269	279	287	292	298
32	249	254	260	269	279	288	298	303	308
33	257	262	269	278	288	298	308	313	319
34	265	270	277	287	298	308	318	324	330
35	273	279	286	297	307	318	329	335	342
36	282	287	294	306	317	329	340	346	353
37	290	296	304	316	328	340	352	358	365
38	299	306	313	326	338	351	364	371	378
39	309	316	324	337	350	363	377	384	392
40	319	327	335	349	363	377	391	399	406

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Influence of Clinical Conditions on Growth Percentiles

Participants for whom clinical conditions occurred during pregnancy and childbirth were retained in the study. We then assessed the effect of excluding them on the parameter estimates of the quantiles. We excluded successively maternal conditions, fetal malformations, and neonatal conditions and assessed the fit for the global EFW percentiles. The parameter estimates obtained were indistinguishable.

In order to illustrate variation of the clinically relevant 10th and 90th percentiles for EFW, we compiled the values (without any formal comparison) for 24, 28, 32, and 36 wk of gestation from the present study, the NICHD Fetal Growth Studies [19], a study from D. R. Congo [30], and another study from Norway [31] (Table 16). Since the other existing multinational study, the Fetal Growth Longitudinal Study of the Intergrowth-21st Project, did not publish EFW but rather AC, which is a major determinant for EFW, we also compiled 10th and 90th percentiles for AC from relevant studies [18,19,30,32–34] (Table 17).

Discussion

In this paper we present the WHO fetal growth charts for EFW and common ultrasound biometric measurements intended for international use. They reveal a wide range of variation in

Table 9. Growth chart for fetal femur length.

Gestational Age (Weeks)	Femur Length (mm) by Percentile								
	2.5	5	10	25	50	75	90	95	97.5
14	10	10	11	12	13	14	15	16	17
15	12	13	14	15	16	17	18	19	20
16	15	16	17	18	19	20	22	22	23
17	19	19	20	21	22	24	25	26	26
18	22	22	23	24	26	27	28	29	30
19	25	26	26	28	29	30	31	32	33
20	28	29	30	31	32	33	35	35	36
21	31	32	33	34	35	36	38	38	39
22	34	35	35	37	38	39	40	41	42
23	36	37	38	39	41	42	43	44	45
24	39	40	41	42	43	45	46	47	47
25	41	42	43	44	46	47	48	49	50
26	43	44	45	46	48	49	51	51	52
27	46	46	47	49	50	52	53	54	55
28	48	48	49	51	52	54	55	56	57
29	50	50	51	53	54	56	57	58	59
30	51	52	53	55	56	58	60	60	61
31	53	54	55	57	59	60	62	63	64
32	55	56	57	59	61	62	64	65	66
33	57	58	60	61	63	65	66	67	68
34	59	60	61	63	65	67	68	69	70
35	61	62	63	65	67	69	70	71	73
36	63	64	65	67	69	70	72	73	75
37	65	66	67	68	70	72	74	75	76
38	66	67	68	70	72	74	75	77	78
39	67	68	69	70	73	75	76	78	79
40	68	68	69	70	73	75	77	78	79

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human fetal growth across different parts of the world. Significant differences in fetal growth between countries are confirmed by differences in birthweight. Furthermore, the study shows that intrauterine growth is influenced by fetal sex and by maternal age, height, weight, and parity, although these influences explain only partially the differences in growth between countries.

The primary motivation for this study, the fetal component of the WHO Multicentre Growth Reference Study [11], was the need for clinical reference intervals applicable internationally, including for areas of the world where perinatal morbidity and mortality are high, hence the multinational design. Driven by the same motivation, we prioritized ultrasound measurements in common clinical use worldwide, the most prominent being EFW (Fig 1; Table 11). The use of estimated weight in grams is simple and intelligible, which enhances clinical management, facilitates communication within the health care system, and is valuable when counselling patients. In addition to the other common measurements in daily use (BPD, HC, AC, and FL) (Fig 1; Tables 6–9), we established reference intervals for the ratios FL/HC and FL/BPD aimed at facilitating the identification and monitoring of disproportionate fetal head development, e.g., hydrocephaly or microcephaly (Fig 1; Tables 12 and 13). The diagnosis in pregnancies complicated by such conditions is often hampered by uncertainty about gestational age since head size (BPD and HC) is also commonly used for the dating of the

Table 10. Growth chart for fetal humerus length.

Gestational Age (Weeks)	Humerus Length (mm) by Percentile								
	2.5	5	10	25	50	75	90	95	97.5
14	10	11	11	12	14	15	16	16	17
15	13	13	14	15	16	18	19	19	20
16	16	16	17	18	19	21	22	22	23
17	19	19	20	21	23	24	25	25	26
18	22	22	23	24	26	27	28	28	29
19	25	25	26	27	28	30	31	31	32
20	27	28	29	30	31	32	33	34	35
21	30	31	31	33	34	35	36	37	38
22	32	33	34	35	36	37	39	39	40
23	34	35	36	37	38	40	41	42	42
24	36	37	38	39	41	42	43	44	45
25	38	39	40	41	42	44	45	46	47
26	40	41	42	43	44	46	47	48	49
27	42	43	43	45	46	47	49	50	51
28	43	44	45	46	48	49	51	52	52
29	45	46	47	48	49	51	52	53	54
30	46	47	48	50	51	53	54	55	56
31	48	49	50	51	53	54	56	57	58
32	49	50	51	53	54	56	57	59	59
33	51	52	53	54	56	58	59	60	61
34	53	53	54	56	58	59	61	62	63
35	54	55	56	57	59	61	62	63	64
36	55	56	57	59	61	62	64	65	66
37	56	57	58	60	62	64	65	66	67
38	57	58	59	61	63	65	66	67	68
39	58	59	60	62	64	65	67	68	69
40	57	58	60	62	64	66	68	69	69

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pregnancy. FL/HC and particularly FL/BPD are less dependent on gestational age after 20 wk of gestation (Fig 1) and may therefore have diagnostic utility.

A strength of the new growth charts provided by the study (Tables 6–15) is that they are based on multinational data, i.e., ten countries, and therefore are more likely to be applicable internationally than previously published reference intervals for EFW based on single countries. A recent sizeable study found significant variation in fetal growth between Asian, black, Hispanic, and white ethnic groups, with Asian fetuses being the smallest and white fetuses the largest, justifying ethnic-specific growth charts [19]. However, that study was confined to the US. Table 16 demonstrates the relation between studies for the clinically important 10th and 90th percentiles for EFW. The WHO growth chart for all countries lies in the middle of them. Although the present study was not designed to investigate ethnic differences, a limited record of participants' ethnicity showed a distribution largely according to country (Table 2). Interestingly, there was a significant difference in the growth of EFW between countries that was not explained by maternal factors (Fig 3; S2 Table). While ethnic differences may play a role in this variation, as for the US-based study [19], variation could also be due to differences in diet and cultural and socioeconomic factors commonly associated with particular ethnic groups. These may also have played a role in the US-based study.

Table 11. Growth chart for estimated fetal weight regardless of fetal sex.

Gestational Age (Weeks)	Estimated Fetal Weight (g) by Percentile								
	2.5	5	10	25	50	75	90	95	97.5
14	70	73	78	83	90	98	104	109	113
15	89	93	99	106	114	124	132	138	144
16	113	117	124	133	144	155	166	174	181
17	141	146	155	166	179	193	207	217	225
18	174	181	192	206	222	239	255	268	278
19	214	223	235	252	272	292	313	328	340
20	260	271	286	307	330	355	380	399	413
21	314	327	345	370	398	428	458	481	497
22	375	392	412	443	476	512	548	575	595
23	445	465	489	525	565	608	650	682	705
24	523	548	576	618	665	715	765	803	830
25	611	641	673	723	778	836	894	938	970
26	707	743	780	838	902	971	1,038	1,087	1,125
27	813	855	898	964	1,039	1,118	1,196	1,251	1,295
28	929	977	1,026	1,102	1,189	1,279	1,368	1,429	1,481
29	1,053	1,108	1,165	1,251	1,350	1,453	1,554	1,622	1,682
30	1,185	1,247	1,313	1,410	1,523	1,640	1,753	1,828	1,897
31	1,326	1,394	1,470	1,579	1,707	1,838	1,964	2,046	2,126
32	1,473	1,548	1,635	1,757	1,901	2,047	2,187	2,276	2,367
33	1,626	1,708	1,807	1,942	2,103	2,266	2,419	2,516	2,619
34	1,785	1,872	1,985	2,134	2,312	2,492	2,659	2,764	2,880
35	1,948	2,038	2,167	2,330	2,527	2,723	2,904	3,018	3,148
36	2,113	2,205	2,352	2,531	2,745	2,959	3,153	3,277	3,422
37	2,280	2,372	2,537	2,733	2,966	3,195	3,403	3,538	3,697
38	2,446	2,536	2,723	2,935	3,186	3,432	3,652	3,799	3,973
39	2,612	2,696	2,905	3,135	3,403	3,664	3,897	4,058	4,247
40	2,775	2,849	3,084	3,333	3,617	3,892	4,135	4,312	4,515

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Another recently published multinational study by the Intergrowth-21st Project presented biometric growth but not EFW data [18]. We therefore present variation in AC, which is closely linked to EFW and is an important predictor of perinatal outcome [6], for the commonly used cutoffs, the 10th and 90th percentiles (Table 17). Interestingly, the 10th percentile for the Intergrowth-21st Project results seems to fall below that of the WHO study, even though the Intergrowth-21st Project study was carried out according to a strictly “prescriptive” concept to establish so-called optimal fetal growth (low-risk pregnancies with no environmental and nutritional constraints, and excluding all conditions during pregnancy and childbirth that may be associated with effects on fetal growth). The WHO study had a similar recruitment but retained in the analysis pregnancies with maternal, fetal, and neonatal clinical conditions, based on the principle that reference intervals should reflect as closely as possible the population to which they will be applied. Furthermore, we assessed the effect of removing such pregnancies from the dataset and found no identifiable effect on the percentiles. As seen from Table 17, it is as if rigorous selection and exclusions have limited effect, and other uncontrolled factors are responsible for the variation between studies and countries. Apart from random error, systematic error due to differences in ultrasound measurement techniques could influence the differences between the studies. However, these studies had well-trained ultrasound

Table 12. Growth chart for fetal femur length/head circumference ratio.

Gestational Age (Weeks)	Femur Length/Head Circumference Ratio by Percentile								
	2.5	5	10	25	50	75	90	95	97.5
14	0.50	0.52	0.53	0.54	0.56	0.57	0.59	0.59	0.60
15	0.54	0.55	0.56	0.57	0.59	0.60	0.61	0.62	0.62
16	0.57	0.58	0.59	0.60	0.61	0.62	0.63	0.64	0.64
17	0.60	0.60	0.61	0.62	0.63	0.64	0.65	0.65	0.66
18	0.62	0.62	0.63	0.64	0.65	0.66	0.66	0.67	0.67
19	0.64	0.64	0.65	0.65	0.66	0.67	0.68	0.68	0.68
20	0.65	0.66	0.66	0.67	0.67	0.68	0.69	0.69	0.69
21	0.66	0.67	0.67	0.68	0.68	0.69	0.69	0.70	0.70
22	0.67	0.67	0.68	0.68	0.69	0.69	0.70	0.70	0.71
23	0.68	0.68	0.68	0.69	0.69	0.70	0.70	0.71	0.71
24	0.68	0.69	0.69	0.69	0.70	0.70	0.71	0.71	0.71
25	0.69	0.69	0.69	0.70	0.70	0.71	0.71	0.71	0.72
26	0.69	0.69	0.69	0.70	0.70	0.71	0.71	0.72	0.72
27	0.69	0.69	0.70	0.70	0.71	0.71	0.72	0.72	0.72
28	0.69	0.70	0.70	0.70	0.71	0.71	0.72	0.72	0.72
29	0.70	0.70	0.70	0.71	0.71	0.72	0.72	0.72	0.73
30	0.70	0.70	0.70	0.71	0.71	0.72	0.72	0.73	0.73
31	0.70	0.70	0.71	0.71	0.72	0.72	0.73	0.73	0.73
32	0.70	0.71	0.71	0.72	0.72	0.73	0.73	0.73	0.74
33	0.71	0.71	0.71	0.72	0.72	0.73	0.73	0.74	0.74
34	0.71	0.71	0.72	0.72	0.73	0.73	0.74	0.74	0.74
35	0.71	0.72	0.72	0.73	0.73	0.74	0.74	0.74	0.75
36	0.72	0.72	0.72	0.73	0.73	0.74	0.74	0.75	0.75
37	0.72	0.72	0.73	0.73	0.74	0.74	0.74	0.75	0.75
38	0.72	0.72	0.73	0.73	0.74	0.74	0.75	0.75	0.75
39	0.72	0.72	0.73	0.73	0.74	0.74	0.75	0.75	0.75
40	0.71	0.72	0.72	0.73	0.73	0.74	0.75	0.75	0.75

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operators specifically instructed for the research procedure using internationally accepted techniques, and this should minimize such error.

Another strength of the present WHO study is the use of quantile regression to establish the reference intervals. Quantile regression makes an inference about regression coefficients for the conditional quantiles of a variable without making assumptions about its distribution: there is no need to assume a particular distribution and to estimate its moments. In consequence, it provides a more direct representation of the observed measurements. This is nicely demonstrated in a recent large study establishing population-specific fetal growth charts [35]. The technique is especially useful when the quantiles vary differently with a covariate such as, in the present study, gestational age. In addition, the method is robust against the effect of outliers and can capture important features of the data that might be missed by models that average across the conditional distribution [25].

Quantile regression is particularly useful in studying distribution changes, and shows in the present study that fetal growth in the population is not symmetrical with gestation. Starting with a higher distribution towards the lower percentiles, EFW shifts to an expanded distribution among the higher percentiles and ends with a noticeable asymmetry near term. The Bowley coefficient for asymmetry changed from -0.016 to $+0.111$ during that period. We are not sure of the nature of the small negative asymmetry in early pregnancy, but speculate that

Table 13. Growth chart for fetal femur length/biparietal diameter.

Gestational Age (Weeks)	Femur Length/Biparietal Diameter Ratio by Percentile								
	2.5	5	10	25	50	75	90	95	97.5
14	0.71	0.72	0.74	0.76	0.78	0.80	0.82	0.83	0.84
15	0.75	0.76	0.77	0.79	0.81	0.83	0.84	0.85	0.86
16	0.79	0.80	0.81	0.82	0.84	0.85	0.87	0.88	0.88
17	0.82	0.82	0.83	0.85	0.86	0.87	0.89	0.89	0.90
18	0.84	0.85	0.85	0.87	0.88	0.89	0.90	0.91	0.91
19	0.86	0.86	0.87	0.88	0.89	0.90	0.91	0.92	0.92
20	0.87	0.88	0.88	0.89	0.90	0.91	0.92	0.93	0.93
21	0.88	0.89	0.89	0.90	0.91	0.92	0.93	0.93	0.94
22	0.89	0.89	0.90	0.91	0.92	0.92	0.93	0.94	0.94
23	0.89	0.90	0.90	0.91	0.92	0.93	0.94	0.94	0.95
24	0.90	0.90	0.91	0.91	0.92	0.93	0.94	0.94	0.95
25	0.90	0.90	0.91	0.92	0.92	0.93	0.94	0.94	0.95
26	0.90	0.91	0.91	0.92	0.93	0.93	0.94	0.95	0.95
27	0.90	0.91	0.91	0.92	0.93	0.93	0.94	0.95	0.95
28	0.90	0.91	0.91	0.92	0.93	0.94	0.94	0.95	0.95
29	0.90	0.91	0.91	0.92	0.93	0.94	0.94	0.95	0.95
30	0.91	0.91	0.91	0.92	0.93	0.94	0.94	0.95	0.95
31	0.91	0.91	0.92	0.92	0.93	0.94	0.95	0.95	0.95
32	0.91	0.91	0.92	0.93	0.93	0.94	0.95	0.95	0.96
33	0.91	0.92	0.92	0.93	0.94	0.94	0.95	0.96	0.96
34	0.92	0.92	0.92	0.93	0.94	0.95	0.95	0.96	0.96
35	0.92	0.92	0.93	0.93	0.94	0.95	0.95	0.96	0.96
36	0.92	0.93	0.93	0.94	0.94	0.95	0.96	0.96	0.97
37	0.92	0.93	0.93	0.94	0.94	0.95	0.96	0.96	0.97
38	0.92	0.93	0.93	0.94	0.95	0.95	0.96	0.96	0.97
39	0.92	0.92	0.93	0.94	0.94	0.95	0.96	0.96	0.97
40	0.91	0.92	0.92	0.93	0.94	0.95	0.96	0.96	0.97

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regulatory functions, such as the process of maternal constraint of fetal growth, change through gestation, i.e., fetuses in the higher percentiles may be exposed to greater influences, which vary with maternal characteristics. This corroborates the differential effects of covariates across the percentiles shown in [S1 Fig](#). We believe that studying distribution dynamics may yield more information on the control of fetal growth.

The study confirmed the biologically interesting facts that fetal sex and maternal height, weight, parity, and age significantly influence fetal growth [31,36,37]. Together with the country differences, the ethnic differences shown in the US population [19], and, not least, the substantial variation in birthweight among carefully selected low-risk pregnancies, these findings document a diversity and plasticity in human prenatal growth dynamics that is only partially understood. There is increasing evidence linking fetal development, and proxies of development such as birthweight, to postnatal health and life course risk of disease [7,9]. This issue is prioritized by the UN and WHO at a time when noncommunicable diseases are becoming global epidemics [10,38]. For example, in our study, birthweights in India were significantly lower than in the other countries, and Indian participants also had the lowest fetal growth and were the shortest mothers. It is known that body composition in Indian newborns contains relatively more fat [39], a pattern that passes across generations [40] and that is linked to

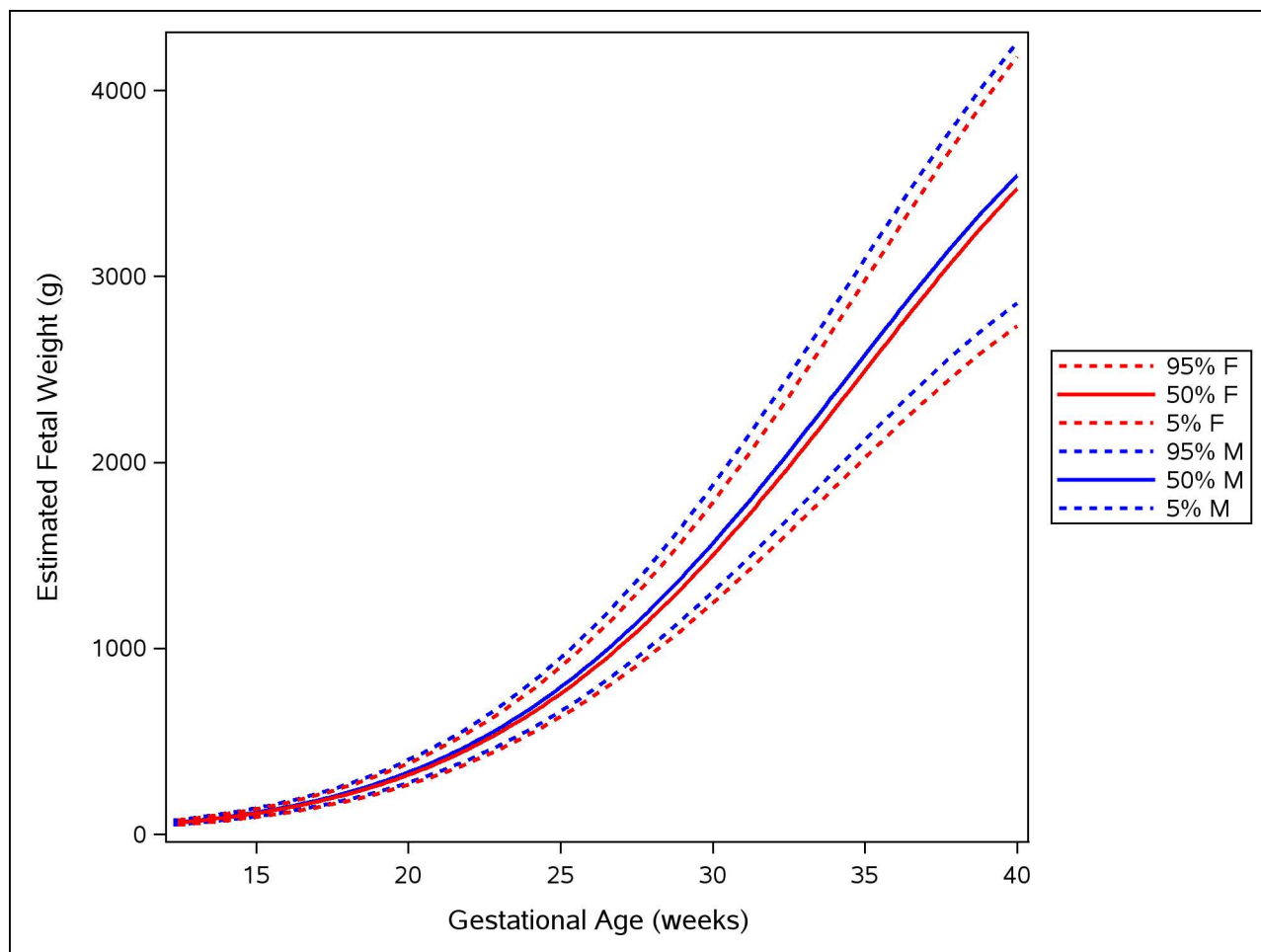


Fig 2. Female and male growth of estimated fetal weight during gestational weeks 14–40. The difference in growth for female (F; red) and male (M; blue) fetuses is shown by the 5th, 50th, and 95th percentiles for EFW growth. The smoothed lines are based on quantile regression that includes data from all the participating countries.

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increased risk of subsequent type 2 diabetes [41]. It seems clear that the understanding of “optimal” fetal growth needs to incorporate more than birthweight.

To have a single fetal growth chart that fits all pregnancies across the world would require that all fetuses had the same genetic background for growth, that this genetic background was reliably expressed in the mother, and that influences such as nutrition, physical activity, stress, toxicants, and other environmental conditions had similar effects on the genotype in all embryos and fetuses. This is very unlikely: recent research has revealed a range of interactions between the developmental environment and genetic and epigenetic processes [9]. Even influences on fetal growth classically thought to be primarily genetic, such as maternal and paternal height, are complicated by environmental factors. Altitude, climate, geography, other environmental conditions, and the challenges of daily life and nutrition vary around the world. Humans adapt across generations to local conditions, and fetal development adds an important adaptive refinement for the next generation. Secular changes in birthweight and child growth patterns have been shown to accompany social changes [42,43]. Fetal growth charts may thus need to be adjusted to fit the diversity of individuals and populations if they are to be of the greatest clinical utility.

Table 14. Growth chart for estimated fetal weight for female fetuses.

Gestational Age (Weeks)	Female Estimated Fetal Weight (g) by Percentile						
	5	10	25	50	75	90	95
14	73	77	82	89	96	102	107
15	92	97	104	113	121	129	135
16	116	122	131	141	152	162	170
17	145	152	164	176	189	202	211
18	180	188	202	217	233	248	261
19	221	231	248	266	285	304	319
20	269	281	302	322	346	369	387
21	324	339	364	388	417	444	466
22	388	405	435	464	499	530	557
23	461	481	516	551	592	629	660
24	542	567	608	649	697	740	776
25	634	663	710	758	815	865	907
26	735	769	823	880	946	1,003	1,051
27	846	886	948	1,014	1,090	1,156	1,210
28	967	1,013	1,083	1,160	1,247	1,323	1,383
29	1,096	1,150	1,230	1,319	1,418	1,505	1,570
30	1,234	1,296	1,386	1,489	1,601	1,699	1,770
31	1,379	1,451	1,553	1,670	1,796	1,907	1,984
32	1,530	1,614	1,728	1,861	2,002	2,127	2,209
33	1,687	1,783	1,911	2,060	2,217	2,358	2,445
34	1,847	1,957	2,101	2,268	2,440	2,598	2,690
35	2,008	2,135	2,296	2,481	2,669	2,846	2,943
36	2,169	2,314	2,494	2,698	2,902	3,099	3,201
37	2,329	2,493	2,695	2,917	3,138	3,357	3,462
38	2,484	2,670	2,896	3,136	3,373	3,616	3,725
39	2,633	2,843	3,096	3,354	3,605	3,875	3,988
40	2,775	3,010	3,294	3,567	3,832	4,131	4,247

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While including ten countries in the present WHO study was a strength compared to previous studies, it still has limitations. The ten population samples, including two in South-East Asia and two in Africa, were included to increase generalizability, but they are still a very limited sample of the global human population. Africa alone has a greater genetic diversity than has the rest of the world [44], and anthropometric variation on that continent is substantial. The present study showed population differences within the pooled dataset, and so the extent to which the results can be extrapolated to other populations, which possibly have other growth dynamics, is at present unknown.

A limitation of the study is that ultrasound measurements were accompanied by a corresponding gestational age exposed on the screen, which could have led to undue changes in the management of the pregnancy and pregnancy duration. However, it was common practice among the sonographers and midwives doing the examination not to pay attention to this gestational age because the department was using other reference values than the one on the screen. On the other hand, part of the ethical commitment of the study was actually to let the mother be informed of any abnormality or deviation of importance discovered, so that it could be taken into account for the management of the pregnancy, and to refer the case to the managing clinician. However, the reported referrals were few and were found not to influence the statistics.

Table 15. Growth chart for estimated fetal weight (EFW) for male fetuses.

Gestational Age (Weeks)	Male Estimated Fetal Weight (g) by Percentile						
	5	10	25	50	75	90	95
14	75	79	84	92	99	105	109
15	96	100	107	116	126	134	139
16	121	127	136	146	158	169	175
17	152	158	170	183	197	210	219
18	188	196	210	226	243	260	271
19	232	241	258	277	298	320	333
20	282	293	314	337	362	389	405
21	341	354	380	407	436	469	489
22	408	424	454	487	522	561	586
23	484	503	539	578	619	666	695
24	570	592	635	681	730	785	818
25	666	692	742	795	853	917	956
26	772	803	860	923	990	1,063	1,109
27	888	924	989	1,063	1,141	1,224	1,276
28	1,014	1,055	1,129	1,215	1,305	1,399	1,458
29	1,149	1,197	1,281	1,379	1,482	1,587	1,654
30	1,293	1,349	1,442	1,555	1,672	1,788	1,863
31	1,445	1,509	1,613	1,741	1,874	2,000	2,085
32	1,605	1,677	1,793	1,937	2,085	2,224	2,319
33	1,770	1,852	1,980	2,140	2,306	2,456	2,562
34	1,941	2,032	2,174	2,350	2,534	2,694	2,814
35	2,114	2,217	2,372	2,565	2,767	2,938	3,072
36	2,290	2,404	2,574	2,783	3,002	3,185	3,334
37	2,466	2,591	2,777	3,001	3,238	3,432	3,598
38	2,641	2,778	2,981	3,218	3,472	3,676	3,863
39	2,813	2,962	3,183	3,432	3,701	3,916	4,125
40	2,981	3,142	3,382	3,639	3,923	4,149	4,383

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Pooling data is not ideal in the presence of variation among populations, and a single overall growth chart will only partially reflect the individual populations included. Figs 4 and 5 show the variation of country-specific percentiles compared with the corresponding overall percentiles of the study and provide an opportunity to assess the magnitude and clinical relevance of the observed variation. Tables 16 and 17 illustrate a similar pattern when compiling the 10th and 90th percentiles for EFW and AC from various relevant high-quality studies available for clinical use. Although no formal statistical comparison was undertaken, the results of these studies illustrate the distribution that can be found around the world. This gives an impression of a wider spread for the 90th percentile than for the 10th. A similar pattern is found within the WHO study itself: a more obvious diversity between the countries for the 90th percentile than for the 10th percentile (Fig 3). As seen from these figures, variation between countries may increase to several hundred grams towards the end of pregnancy, and may cause misclassifications when the overall percentile is used. Secondly, it seems that population variation in growth is more reflected in the 90th percentile than in the lowest percentiles. Thus, it is possible that the 10th, 5th, and 2.5th percentiles of a pooled study are more universally applicable, while the upper percentiles—90th, 95th, and 97.5th—vary more according to population

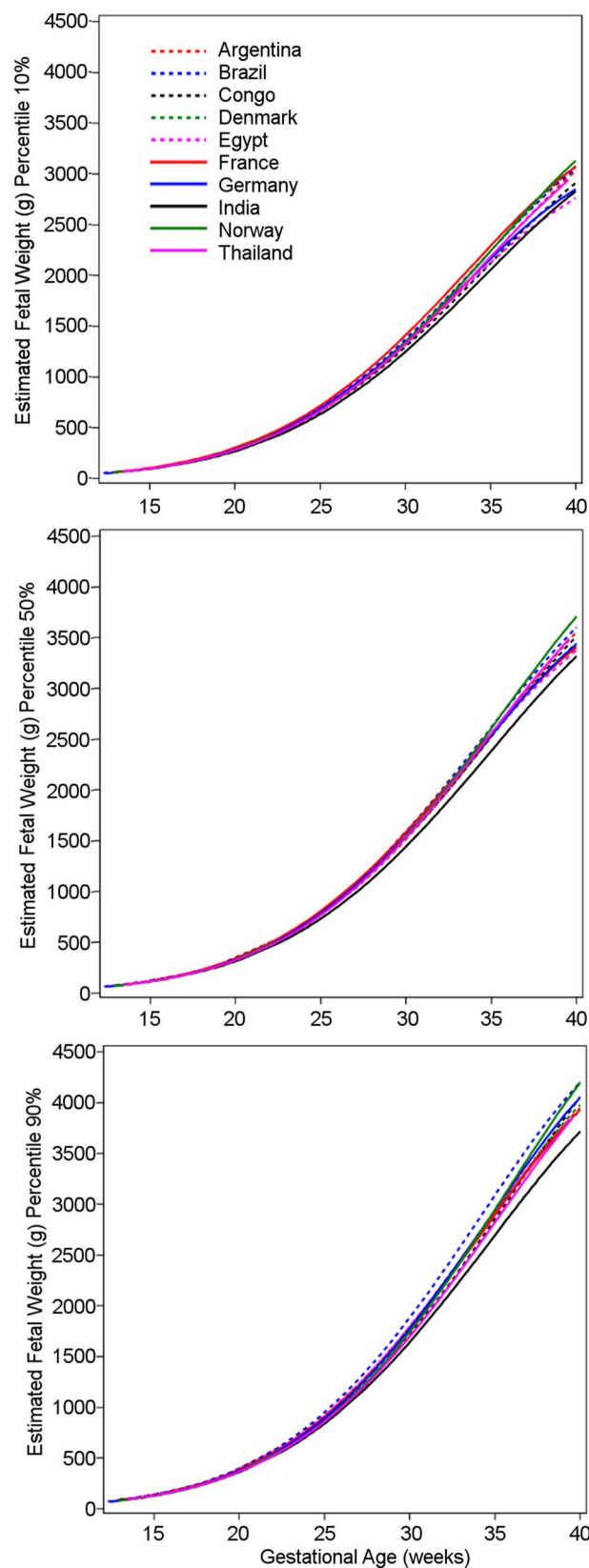


Fig 3. Influence of country on estimated fetal weight. The 10th, 50th, and 90th percentiles for estimated fetal weight in grams for the ten participating countries, with variation due to country becoming more obvious towards the end of gestation. Congo, Democratic Republic of the Congo.

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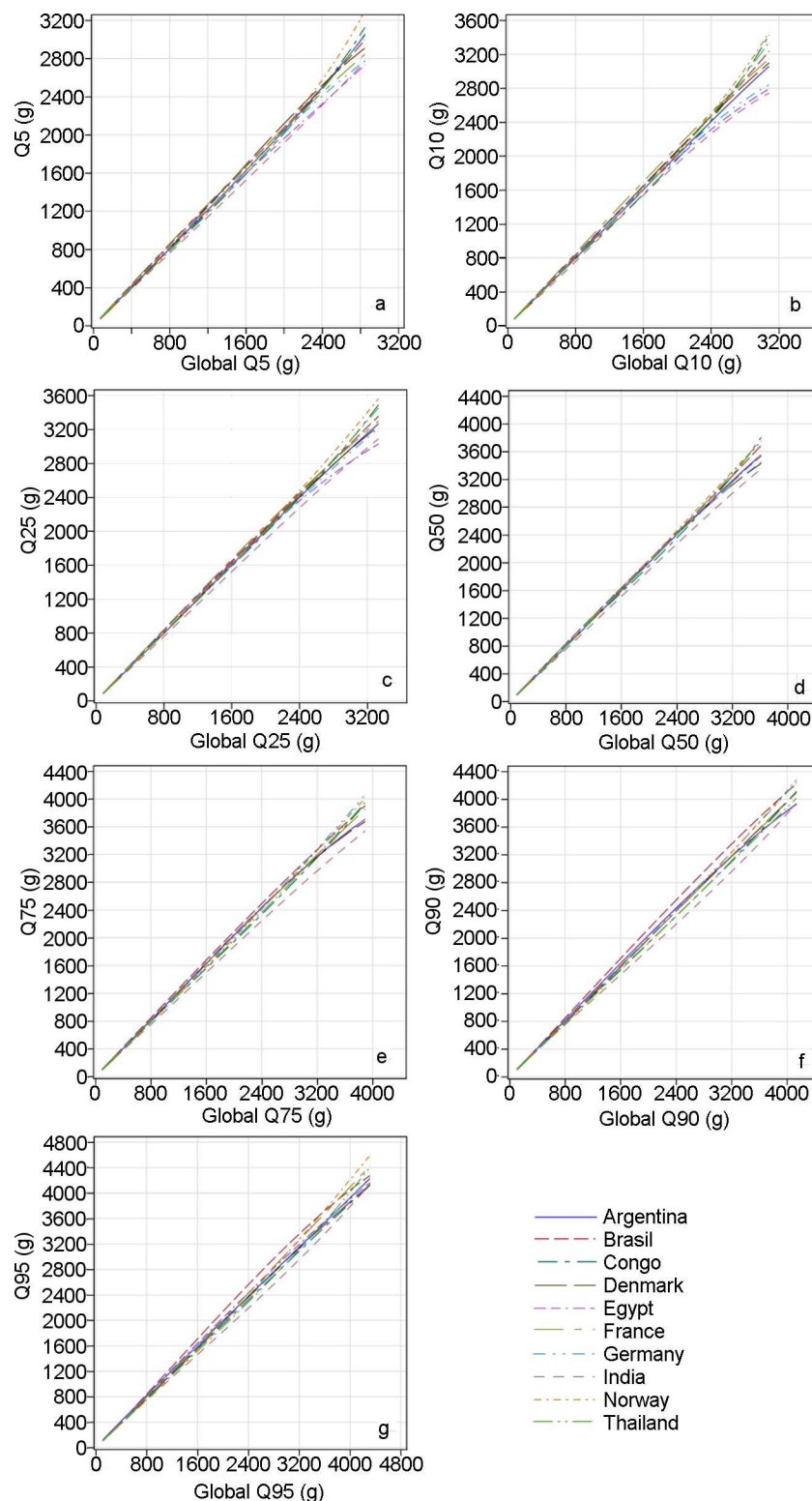


Fig 4. Quantile-quantile plots comparing countries' distributions with the global distribution of estimated fetal weight. The 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles (Q05, Q10, Q25, Q50, Q75, and Q90, respectively) for the distribution of each country are plotted versus the same percentiles of the global distribution (global Q05, global Q10, global Q25, global Q50, global Q75, global Q90, respectively). Congo, Democratic Republic of the Congo.

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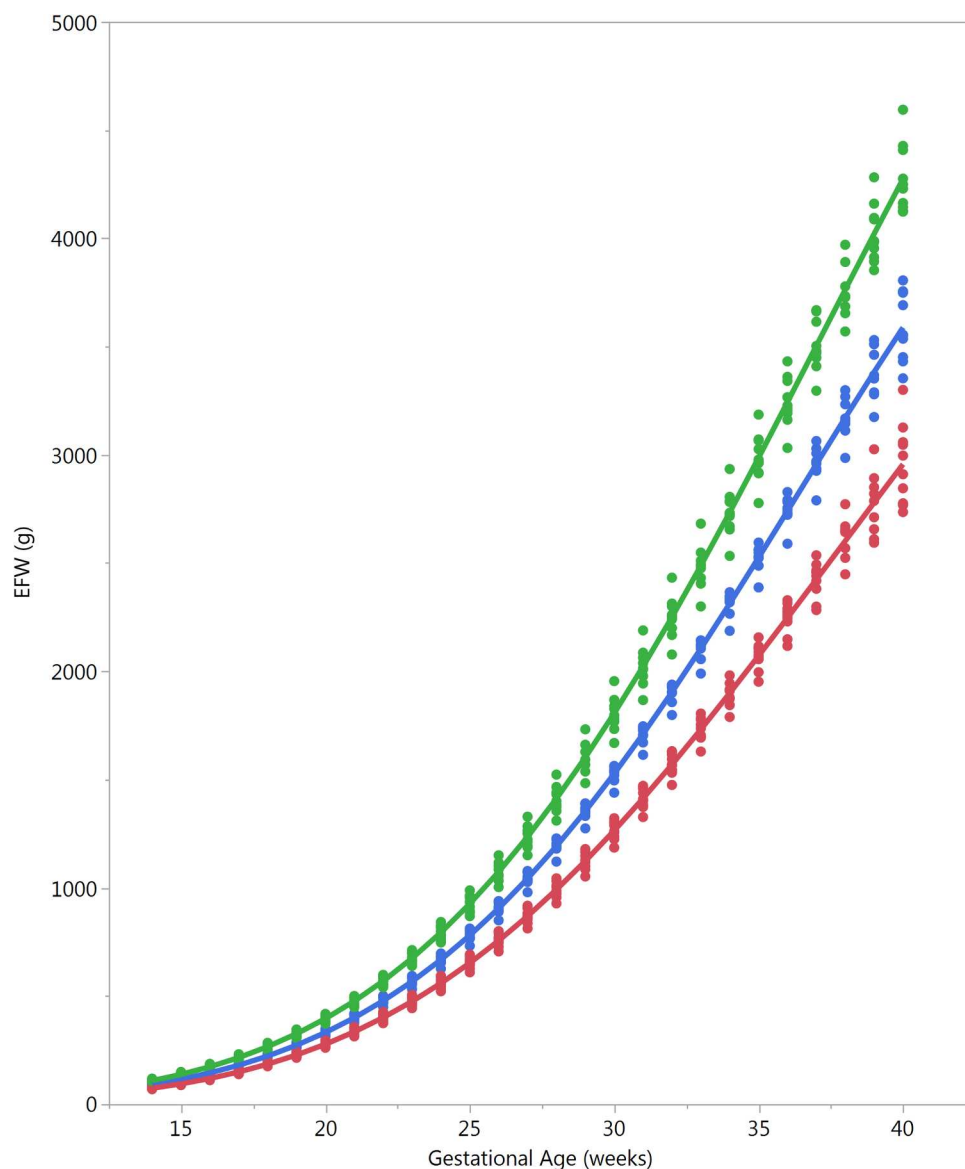


Fig 5. Country differences in estimated fetal weight. Selected percentiles for estimated fetal weight (EFW) for the ten participating countries, showing the magnitude of differences (red, 5th percentile; blue, 50th percentile; green, 95th percentile; each dot denotes a country).

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characteristics and accordingly will be more in need of adjustment, i.e., customization, for use at the population level [37].

It follows that whenever the WHO growth charts, or any reference intervals, are applied to a population, their performance should be checked or tested in order to ensure appropriate use. It is possible to adjust them by changing cutoffs (e.g., from 10th to 5th percentile) to fit clinical needs better, and it is possible to customize the percentiles to country, maternal characteristics, and fetal sex to improve diagnostic performance [45]. A further refinement would be to introduce conditioning terms when using repeated ultrasound measurements for monitoring growth [46,47], i.e., narrowing the expected reference interval for an assessment by conditioning it using a previous measurement. WHO is working on these methods to make them generally available with the growth chart.

Table 16. The 10th and 90th percentile for estimated fetal weight in relation to other relevant reference values.

Reference Chart	Gestational Week				
	20	24	28	32	36
10th percentile of EFW (g)					
US, white [†]	289	583	1,045	1,686	2,432
D. R. Congo [#]	288	576	1,023	1,624	2,310
WHO	286	576	1,026	1,635	2,352
US, black [†]	286	559	985	1,579	2,264
Norway*	283	610	1,102	1,730	2,411
US, Hispanic [†]	279	555	987	1,595	2,298
US, Asian [†]	275	546	978	1,574	2,262
90th percentile of EFW (g)					
Norway*	408	833	1,472	2,304	3,230
US, white [†]	381	771	1,391	2,276	3,368
WHO	380	765	1,368	2,187	3,153
US, Hispanic [†]	379	755	1,353	2,209	3,245
US, black [†]	376	742	1,317	2,135	3,115
US, Asian [†]	373	737	1,318	2,129	3,111
D. R. Congo [#]	345	700	1,277	2,083	3,032

Percentiles from the present multinational study (bold), a recent multiethnic national study in the US [19], a study from D. R. Congo [30], and another study from Norway [31] are listed according to descending values at 20 wk, but are not formally compared or ranked.

[†]Buck Louis et al. [19].

[#]Landis et al. [30].

*Johnsen et al. [31].

D. R., Congo, Democratic Republic of the Congo; EFW, estimated fetal weight.

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If such adjustments and refinements do not suffice to make the growth charts fit clinical needs appropriately, then it may be necessary to establish new high-quality reference intervals for a population. For example, the WHO growth charts and many others are based on populations living at altitudes < 1,500 m. However, millions of people live at higher altitudes, and their physiological adaptations include pregnancy and fetal development. It might be that specific charts will be needed for such populations.

The concept of a “standard,” whether international or national, is often used for instruments and methods to make procedures uniform and to reduce random and systematic error, rather than to set a standard for a biological parameter such as height or bodyweight for the population globally. We are inclined to the view that, while the methodology to define reference ranges or charts for fetal growth needs to be standardized, fetal growth itself is a biological parameter expected to reflect adaptive processes and to change with development, time, location, and environmental conditions. Variation in fetal growth within and between populations should therefore not be ignored.

To apply any growth chart sensibly requires insight, critical attitude, and pragmatism. We believe that the present WHO fetal growth charts can be used internationally, particularly where no local data exist. However, once they are in use, it will be prudent to test the performance of the charts in a particular setting in case adjustments, customization, or replacement with population-specific high-quality reference intervals is needed. With the currently varying degrees of resources, health, and needs around the world, health care professionals have the

Table 17. The 10th and 90th percentile for fetal abdominal circumference in relation to relevant reference values.

Reference Chart	Gestational Week				
	20	24	28	32	36
10th percentile AC (mm)					
US, white [¶]	141	185	227	268	306
WHO	139	184	225	260	294
Norway*	139	182	223	262	299
US, Asian [¶]	139	182	221	260	295
US, Hispanic [¶]	138	181	221	262	299
Intergrowth-21st Project [§]	138	179	219	257	291
US, black [¶]	137	179	217	267	293
Thailand [#]	135	177	217	254	290
UK ^{&}	135	175	213	249	283
90th percentile AC (mm)					
Norway*	165	213	259	303	346
US, white [¶]	164	212	258	306	353
US, Hispanic [¶]	163	210	255	303	349
WHO	161	210	256	298	340
US, Asian [¶]	161	208	252	299	343
Thailand [#]	159	208	256	301	339
US, black [¶]	159	205	249	295	340
UK ^{&}	158	204	248	290	330
Intergrowth-21st Project [§]	158	203	248	291	335

Percentiles from the present multinational study (bold), a recent multinational study (Intergrowth-21st Project), a recent multiethnic study in the US, and three studies from Norway, Thailand, and the United Kingdom are listed according to descending values at 20 wk, but are not formally compared or ranked.

[¶]Buck Louis et al. [19].

*Johnsen et al. [33].

[§]Papageorgiou et al. [18].

[#]Sunsaneevithayakul et al. [34].

[&]Chitty et al. [32].

AC, abdominal circumference; D. R., Congo, Democratic Republic of the Congo.

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responsibility of fitting and refining the use of the fetal growth charts to best serve the population in their care.

Supporting Information

S1 Fig. Influence of covariates on estimated fetal weight quantiles. (A) Intercept; (B) fetal sex; (C) parity; (D) maternal age; (E) maternal weight; (F) maternal height; (G) gestational age linear component; (H) gestational age quadratic component; (I) gestational age cubic component. Output of quantile profilers from quantile multivariate regression in the logarithmic scale, presented as the effect of covariates with 95% confidence bands. For binary variables (sex of the fetus and parity), the relative change is between the two categories; for continuous variables, the relative change refers to the increment in EFW resulting from a unit increment of the independent variable (year for maternal age, kilogram for maternal weight, and centimeter for maternal height). Gestational age was included in the model with polynomial terms (linear, quadratic, and cubic). (DOCX)

S2 Fig. Influence of country on fetal growth expressed as the ultrasound measure biparietal diameter. Graphs of the 10th, 50th, and 90th percentiles for the ultrasound measure BPD in millimeters for the ten participating countries.

(TIF)

S3 Fig. Influence of country on fetal growth expressed as the ultrasound measure head circumference. Graphs of the 10th, 50th, and 90th percentiles for the ultrasound measure HC in millimeters for the ten participating countries.

(TIF)

S4 Fig. Influence of country on fetal growth expressed as the ultrasound measure abdominal circumference. Graphs of the 10th, 50th, and 90th percentiles for the ultrasound measure AC in millimeters for the ten participating countries.

(TIF)

S5 Fig. Influence of country on fetal growth expressed as the ultrasound measure femur length. Graphs of the 10th, 50th, and 90th percentiles for the ultrasound measure FL in millimeters for the ten participating countries.

(TIF)

S6 Fig. Influence of country on fetal growth expressed as the ultrasound measure humerus length. Graphs of the 10th, 50th, and 90th percentiles for the ultrasound measure HL in millimeters for the ten participating countries.

(TIF)

S1 File. Growth charts for the fetal ultrasound measurements biparietal diameter, head circumference, abdominal circumference, femur length, and humerus length; for estimated fetal weight; and for the ratios femur length/head circumference and femur length/biparietal diameter in one Excel file.

(XLSX)

S1 Table. Compliance of ultrasound visits with protocol, measured by observed versus expected.

(DOCX)

S2 Table. Variation of estimated fetal weight quantiles due to country, maternal characteristics (age, height, weight, and parity), and sex of the fetus. Output from quantile multivariate regression showing Wald chi-square tests for gestational age; country; the interaction of gestational age and country; sex of the fetus; and maternal characteristics.

(DOCX)

S3 Table. Variation of estimated fetal weight quantiles due to country, maternal characteristics (age, BMI, and parity), and sex of the fetus. Output from quantile multivariate regression showing Wald chi-square tests for gestational age; country; the interaction of gestational age and country; sex of the fetus; and maternal characteristics.

(DOCX)

S4 Table. Comparison of country percentiles with overall percentiles. The 10th, 50th, and 90th percentiles for overall EFW, and the 95% confidence intervals for the difference between each country's percentiles and the overall percentiles at 20, 24, 28, 32, and 36 wk of gestational age. The results should be interpreted with caution (the study was not powered for this analysis; multiplicity of inferences implies that the confidence is much lower than 95%).

(DOCX)

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รายชื่อกลุ่มวิจัย

ชื่อ-นามสกุล	เริ่มเข้าโครงการ			ปัจจุบัน		
	ตำแหน่งวิชาการ	สังกัด	ตำแหน่งในโครงการ	ตำแหน่งวิชาการ	สังกัด	สถานภาพปัจจุบัน
1. ศ.นพ.ภิเศก ลุมพิกานนท์	ศาสตราจารย์	ภาควิชาสูติฯ คณะแพทยศาสตร์ มข.	หัวหน้าโครงการ	ศาสตราจารย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
2. ศ.ดร.มาลินี เหล่าไพบูลย์	ศาสตราจารย์	ภาควิชาชีวสถิติ คณะสาธารณสุขศาสตร์ มข.	ผู้ร่วมวิจัย	ศาสตราจารย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
3. ศ.พญ.เจศฎา ถิ่นคำรพ	ศาสตราจารย์	ภาควิชาสูติฯ คณะแพทยศาสตร์ มข.	ผู้ร่วมวิจัย	ศาสตราจารย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
4. รศ.พญ.ประนอม บุพศิริ	รองศาสตราจารย์	ภาควิชาสูติฯ คณะแพทยศาสตร์ มข.	ผู้ร่วมวิจัย	รองศาสตราจารย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
5. พญ.อุษณีย์ สวัสดิ์พาณิชย์	แพทย์หญิง	กลุ่มงานสูตินรีเวชกรรม โรงพยาบาลขอนแก่น	ผู้ร่วมวิจัย	แพทย์หญิง	โรงพยาบาลศูนย์ขอนแก่น	ยังอยู่ในโครงการ
6. พญ.ทุมวดี ตั้งศิริวัฒนา	แพทย์หญิง	กลุ่มงานสูตินรีเวชกรรม โรงพยาบาลขอนแก่น	ผู้ร่วมวิจัย	แพทย์หญิง	โรงพยาบาลศูนย์ขอนแก่น	ยังอยู่ในโครงการ
7. รศ.เบญจา มุกตพันธ์	รองศาสตราจารย์	ภาควิชาโภชนวิทยา คณะสาธารณสุขศาสตร์ มข.	ผู้ร่วมวิจัย	รองศาสตราจารย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
8. นพ.บรรพจน์ สุวรรณชาติ	นายแพทย์	กลุ่มงานสูตินรีเวชกรรม โรงพยาบาลกาฬสินธุ์	ผู้ร่วมวิจัย	นายแพทย์	โรงพยาบาลกาฬสินธุ์	ยังอยู่ในโครงการ
9. ผศ.พอใจ พัทธินิตย์ธรรม	อาจารย์	ภาควิชาชีวสถิติ คณะสาธารณสุขศาสตร์ มข.	ผู้ร่วมวิจัย	ผู้ช่วยศาสตราจารย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
10. พญ.บุษรินทร์ เขียนมัน	พยาบาล	กลุ่มงานสูตินรีเวชกรรม โรงพยาบาลกาฬสินธุ์	ผู้ร่วมวิจัย	พยาบาล	โรงพยาบาลกาฬสินธุ์	ยังอยู่ในโครงการ
11. นพ.สุทิต คุณประดิษฐ์	นายแพทย์	กลุ่มงานสูตินรีเวชกรรม โรงพยาบาลลำพูน	ผู้ร่วมวิจัย	นายแพทย์	โรงพยาบาลลำพูน	ยังอยู่ในโครงการ
12. พญ.ศิริวรรณ ตั้งจิตกมล	แพทย์หญิง	วิทยาลัยแพทยศาสตร์กรุงเทพมหานคร	ผู้ร่วมวิจัย	แพทย์หญิง	วิทยาลัยแพทยศาสตร์กรุงเทพมหานคร	ยังอยู่ในโครงการ
13. รศ.พญ.ทิพวรรณ เลียบสือตระกูล	รองศาสตราจารย์	ภาควิชาสูติฯ คณะแพทยศาสตร์ มอ.	ผู้ร่วมวิจัย	รองศาสตราจารย์	มหาวิทยาลัยสงขลานครินทร์	ยังอยู่ในโครงการ
14. รศ.นพ.ยุทธพงศ์ วีระวัฒน์ตระกูล	รองศาสตราจารย์	ภาควิชาสูติฯ คณะแพทยศาสตร์ มข.	ผู้ร่วมวิจัย	รองศาสตราจารย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
15. อ.นพ.เกียรติศักดิ์ คงวัฒนกุล	อาจารย์	ภาควิชาสูติฯ คณะแพทยศาสตร์ มข.	ผู้ร่วมวิจัย	อาจารย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
16. อ.นพ.เจน โสธรวิทย์	อาจารย์	ภาควิชาสูติฯ คณะแพทยศาสตร์ มข.	ผู้ร่วมวิจัย	อาจารย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
17. รศ.นพ.วิทยา ธิฐาพันธ์	รองศาสตราจารย์	ภาควิชาสูติฯ คณะแพทยศาสตร์ศิริราชพยาบาล	ผู้ร่วมวิจัย	รองศาสตราจารย์	มหาวิทยาลัยมหิดล	ยังอยู่ในโครงการ
18. รศ.พญ.สายฝน ชาวาลไพบูลย์	รองศาสตราจารย์	ภาควิชาสูติฯ คณะแพทยศาสตร์ศิริราชพยาบาล	ผู้ร่วมวิจัย	รองศาสตราจารย์	มหาวิทยาลัยมหิดล	ยังอยู่ในโครงการ

หมายเหตุ

สังกัด

ให้ใส่รายละเอียดที่อยู่ต้นสังกัด เช่น ภาควิชา / คณะ / มหาวิทยาลัย

สถานภาพปัจจุบัน

- ยังอยู่ในโครงการหรือไม่ หากไม่อยู่ในโครงการแล้ว ให้ระบุหน่วยงานใหม่ด้วย

- หากเริ่มเข้าโครงการเป็นนักศึกษาปริญญาเอก ปริญญาโท หรือปริญญาตรี ให้ระบุปัจจุบันสำเร็จการศึกษาหรือยังไม่สำเร็จการศึกษา

รายชื่อกลุ่มวิจัยใหม่

ชื่อ-นามสกุล	เริ่มเข้าโครงการ			ปัจจุบัน		
	ตำแหน่งวิชาการ	สังกัด	ตำแหน่งในโครงการ	ตำแหน่งวิชาการ	สังกัด	สถานภาพปัจจุบัน
1. รศ.นพ.ชานัญ เกียรติพิริสกุล	รองศาสตราจารย์	ภาควิชาสูติฯ คณะแพทยศาสตร์ มข.	ผู้ร่วมวิจัย	รองศาสตราจารย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
2. อ.อมรรัตน์ สุโพธิ์เคน	อาจารย์	ภาควิชาสูติฯ คณะแพทยศาสตร์ มข.	ผู้ร่วมวิจัย	อาจารย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
3. นพ.กฤษ สาลัง	อาจารย์	กลุ่มงานออร์โธปิดิกส์ โรงพยาบาลขอนแก่น	ผู้ร่วมวิจัย	อาจารย์	โรงพยาบาลขอนแก่น	ยังอยู่ในโครงการ
4. ดร.อนุชนรา ตาลกุล คัสเธอร์	อาจารย์	ภาควิชาชีวสถิติฯ คณะสาธารณสุขศาสตร์ มข.	ผู้ร่วมวิจัย	อาจารย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
5. พญ.ภัสสรวิทย์ รังสิปการการ	แพทย์หญิง		ผู้ร่วมวิจัย	แพทย์หญิง		ยังอยู่ในโครงการ
6. พญ.หลิงหลิง สาลัง	อาจารย์	ภาควิชาสูติฯ คณะแพทยศาสตร์ มข.	ผู้ร่วมวิจัย	อาจารย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
7. นพ.ณัฐพงษ์ ก้านคูณ	นายแพทย์	ภาควิชาสูติฯ คณะแพทยศาสตร์ มข.	ผู้ร่วมวิจัย	นายแพทย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
8. นพ.คมสันต์ ชำรงอนันตสกุล	อาจารย์	ภาควิชารังสีวิทยา คณะแพทยศาสตร์ มข.	ผู้ร่วมวิจัย	อาจารย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
9. นพ.นฤดม ศุภะกะลิน	อาจารย์	ภาควิชารังสีวิทยา คณะแพทยศาสตร์ มข.	ผู้ร่วมวิจัย	อาจารย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
10. ผศ.พญ.ศรีนารี แก้วฤดี	ผู้ช่วยศาสตราจารย์	ภาควิชาสูติฯ คณะแพทยศาสตร์ มข.	ผู้ร่วมวิจัย	ผู้ช่วยศาสตราจารย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
11. รศ.นพ.ยอดยิ่ง ปัญจสวัสดิ์วงศ์	รองศาสตราจารย์	ภาควิชาวิสัญญีวิทยา คณะแพทยศาสตร์ มข.	ผู้ร่วมวิจัย	รองศาสตราจารย์	มหาวิทยาลัยเชียงใหม่	ยังอยู่ในโครงการ
12. อ.นพ.ธีระยุทธ เต็มธนะกิจไพศาล	อาจารย์	ภาควิชาสูติฯ คณะแพทยศาสตร์ มข.	ผู้ร่วมวิจัย	อาจารย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
13. อ.นพ.อภิวัฒน์ เอื้ออังกูร	อาจารย์	ภาควิชาสูติฯ คณะแพทยศาสตร์ มข.	ผู้ร่วมวิจัย	อาจารย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
14. อ.นพ.วร ลุสึระ	อาจารย์	ภาควิชาศัลยศาสตร์ คณะแพทยศาสตร์ มข.	ผู้ร่วมวิจัย	อาจารย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
15. อ.นพ.เอกพงศ์ สาริตการมณี	อาจารย์	ภาควิชาศัลยศาสตร์ คณะแพทยศาสตร์ มข.	ผู้ร่วมวิจัย	อาจารย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
16. พญ.นันทสิริ เอี่ยมอุดมการณ์	แพทย์หญิง	ภาควิชาสูติฯ คณะแพทยศาสตร์ มข.	ผู้ร่วมวิจัย	แพทย์หญิง	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
17. ภญ.พันสุข ชูมวรฐาภิ	เภสัชกร	คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น	ผู้ร่วมวิจัย	เภสัชกร	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
18..ผศ.ฉลอง ชิวเกรียงไกร	ผู้ช่วยศาสตราจารย์	ภาควิชาสูติฯ คณะแพทยศาสตร์ มข.	ผู้ร่วมวิจัย	ผู้ช่วยศาสตราจารย์	มหาวิทยาลัยเชียงใหม่	ยังอยู่ในโครงการ

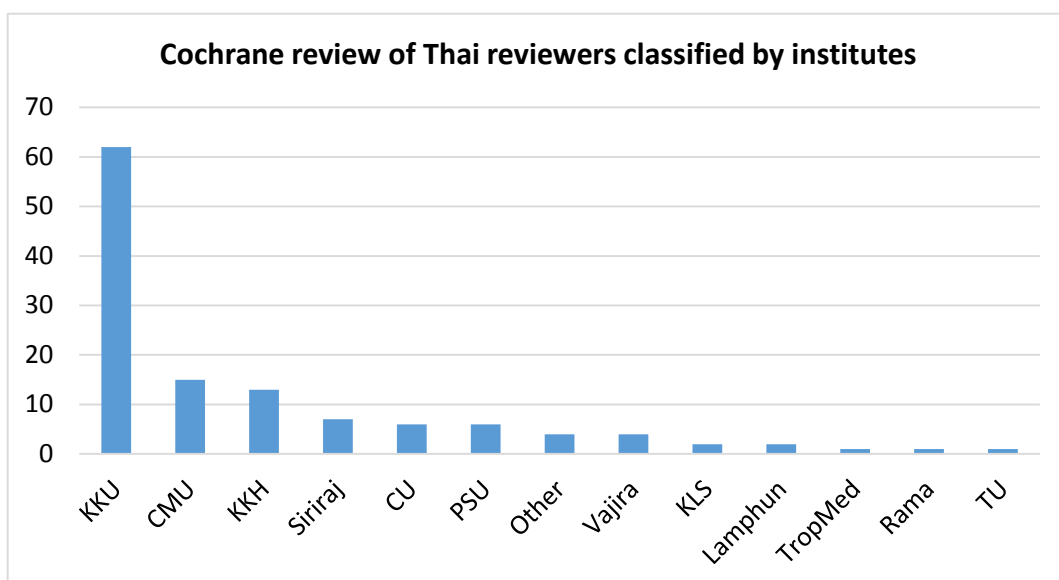
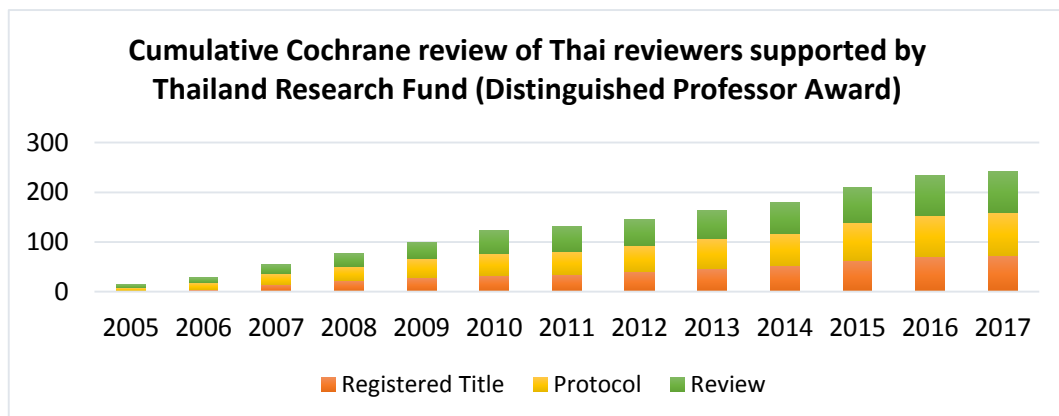
หมายเหตุ

สังกัด

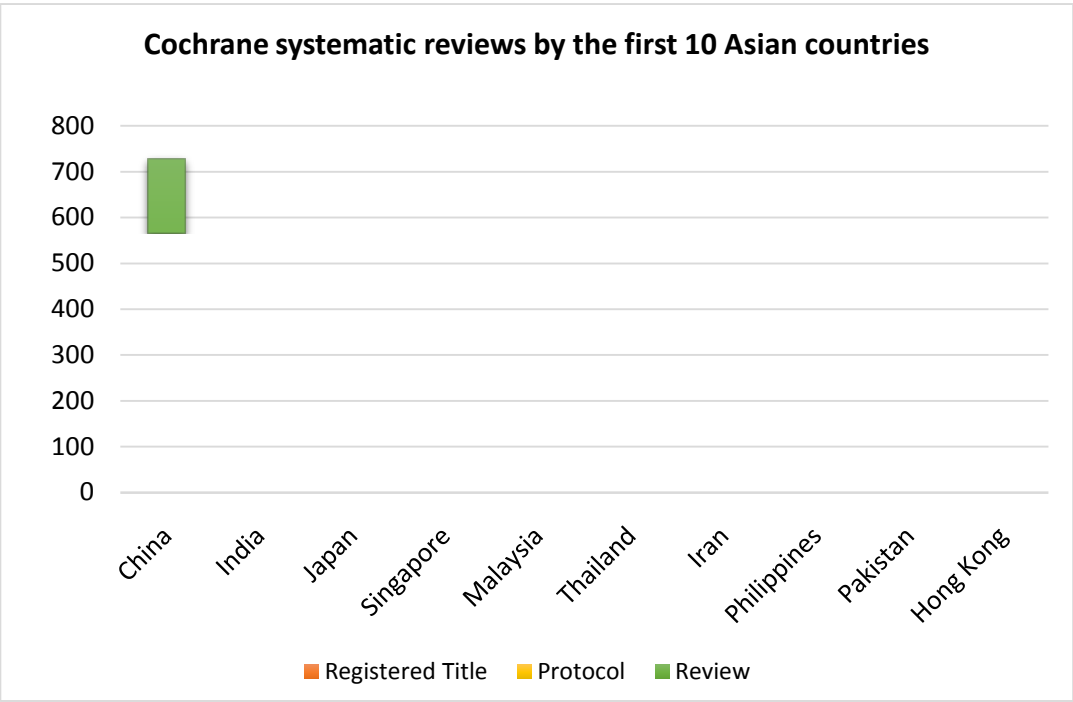
ให้ใส่รายละเอียดที่อยู่ต้นสังกัด เช่น ภาควิชา / คณะ / มหาวิทยาลัย

สถานภาพปัจจุบัน

- ยังอยู่ในโครงการหรือไม่ หากไม่อยู่ในโครงการแล้ว ให้ระบุหน่วยงานใหม่ด้วย
- หากเริ่มเข้าโครงการเป็นนักศึกษาปริญญาเอก ปริญญาโท หรือปริญญาตรี ให้ระบุปัจจุบันสำเร็จการศึกษาหรือยังไม่สำเร็จการศึกษา



Cochrane systematic reviews by the first 10 Asian countries



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