



รายงานวิจัยฉบับสมบูรณ์

โครงการ : สนับสนุนการทำวิจัยเชิงสังเคราะห์ร่วมกับ Cochrane
Collaboration และการวิจัยระบาดวิทยาคลินิก

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ผู้วิจัย ศ.น.พ.ภิเศก ลุมพิกานนท์
ภาควิชาสูติศาสตร์และนรีเวชวิทยา
คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น

สนับสนุนโดยสำนักงานกองทุนสนับสนุนการวิจัย

บทคัดย่อ

ความรู้ทางด้านระบาดวิทยาคลินิกจะช่วยให้นักวิจัยสร้างโครงการวิจัยที่เหมาะสม ดำเนินการวิจัยได้ดีและแปลผลการวิจัยได้ถูกต้อง ซึ่งจะทำให้ผู้วิจัยสามารถตอบคำถามวิจัยต่าง ๆ และนำผลการวิจัยไปใช้ในการดูแลรักษาผู้ป่วยได้อย่างเหมาะสม การดูแลรักษาผู้ป่วยจะต้องเลือกใช้การรักษาพยาบาลที่ได้รับการพิสูจน์โดยการวิจัยที่เชื่อถือได้ว่าให้ผลดีมากกว่าผลเสีย ตามหลักการที่ถูกต้องนักวิชาการไม่สามารถเลือกผลงานวิจัยงานใดงานหนึ่งมาตอบคำถามวิจัยนั้นๆ แต่ควรพิจารณาผลงานวิจัยที่มีคุณภาพดีที่เกี่ยวข้องกับเรื่องนั้น ๆ ทั้งหมด และนำเอาข้อมูลมาสังเคราะห์รวมกันโดยใช้การวิจัยเชิงสังเคราะห์ (Research synthesis) ซึ่งประกอบด้วย ขั้นตอนที่สำคัญ 2 ขั้นตอน ได้แก่ การทบทวนวรรณกรรมอย่างเป็นระบบ (systematic review) และการวิเคราะห์ข้อมูลแบบ meta-analysis การไม่นำผลการวิจัยเชิงสังเคราะห์มาใช้ อาจจะทำให้ผู้ป่วยเสียโอกาสที่จะได้รับการรักษาพยาบาลที่ได้ผลดีหรืออาจจะได้รับการรักษาพยาบาลที่มีผลเสียมากกว่าผลดี อาจจะมีการทำวิจัยที่ไม่จำเป็นเพราะถ้าทำวิจัยเชิงสังเคราะห์โดยใช้งานวิจัยที่มีอยู่ ก็จะได้คำตอบโดยไม่ต้องทำวิจัยแล้ว และทำให้เกิดการใช้ทรัพยากรที่มีอยู่จำกัดอย่างไม่มีประสิทธิภาพ

โครงการนี้มีวัตถุประสงค์เพื่อที่จะผลิตนักวิจัยด้านวิทยาศาสตร์สุขภาพที่มีความสามารถ ทั้งด้าน Clinical epidemiology research และ research synthesis ผลิตงานวิจัยแบบนิพนธ์ต้นฉบับ (Original articles) ที่มีคุณภาพสูงเพื่อตีพิมพ์ในวารสารระดับนานาชาติ และงานวิจัยเชิงสังเคราะห์ เพื่อตีพิมพ์ใน Cochrane Library รวมทั้งดำเนินการให้มีการนำผลงานวิจัยไปใช้อย่างเป็นรูปธรรม

ในระยะเวลา 3 ปีมีนักวิจัยเข้าร่วมในโครงการจำนวน 43 คน จาก 11 สถาบัน มีผลงานตีพิมพ์ใน International journals จำนวน 29 ฉบับ (เป็นงานวิจัย Original articles และบทความใน international peer-reviewed journals จำนวน 17 เรื่อง และงานวิจัยเชิงสังเคราะห์ใน Cochrane Library จำนวน 12 เรื่อง) และมีการตีพิมพ์ Protocols for Cochrane reviews ใน Cochrane Library อีก 9 เรื่อง

Keywords : การวิจัยเชิงสังเคราะห์ การทบทวนวรรณกรรมอย่างเป็นระบบระบาดวิทยาคลินิก
Cochrane library, meta-analysis

Abstract

Knowledge in clinical epidemiology will help researchers in developing appropriate research proposal, conducting research project and interpreting research results correctly. This will allow clinical researchers to answer clinical questions and therefore can provide appropriate healthcare. Healthcare providers should select interventions that have been proven by reliable research that they do more goods than harm. Theoretically, healthcare providers should not base their decision on the research papers that they like. They must search all papers on that topic that are available, critically appraise them and select only those papers with good quality and synthesize the data together. This is the concept of research synthesis which consists of systematic review and meta-analysis as appropriate. Failure to use research synthesis may cause inappropriate use of resources in healthcare and health research. Patients might not receive effective interventions or might receive ineffective or even harmful interventions.

This program aims to produce researchers competent in Clinical epidemiology research and research syntheses, publishing original articles in international peer reviewed journals and research synthesis in Cochrane Library and promote the implementation of research results in healthcare.

During the three-year period there are 43 researchers from eleven institutes involved in the program. There were 29 papers published in international journal (17 original articles and peer-reviewed journals and 12 papers in Cochrane Library). We also published 9 protocols for Cochrane reviews in Cochrane Library.

Keywords : Clinical epidemiology, research synthesis, systematic review, meta-analysis, Cochrane Library.

Executive Summary

1. ความสำคัญและที่มาของปัญหา

ระบาดวิทยาคลินิกเป็นวิชาพื้นฐานครอบคลุมถึงระเบียบวิธีวิจัยและชีวสถิติ ความรู้ทางด้านระบาดวิทยาคลินิกจะช่วยให้นักวิจัยสร้างโครงการวิจัยที่เหมาะสม ดำเนินการวิจัย ได้ดีและแปลผลการวิจัยได้ถูกต้อง ซึ่งจะทำให้ผู้วิจัยสามารถตอบคำถามวิจัยต่าง ๆ และนำ ผลการวิจัยไปใช้ในการดูแลรักษาผู้ป่วยได้อย่างเหมาะสม

ผู้ให้การดูแลรักษาผู้ป่วยจะต้องเลือกใช้การรักษาพยาบาลที่ได้รับการพิสูจน์โดยการวิจัย ที่เชื่อถือได้ว่าให้ผลดีมากกว่า แต่เดิมเป็นที่ยอมรับว่าการวิจัยแบบ randomized controlled trial (RCT) ที่มีขนาดตัวอย่างเพียงพอเป็นการวิจัยที่ดีที่สุดในการจะตอบคำถามวิจัยชนิดนี้ แต่การทำ วิจัยแบบ RCT ต้องการผู้เชี่ยวชาญที่มีความรู้และประสบการณ์ งบประมาณค่อนข้างสูง และใช้ ระยะเวลาานกว่าจะได้คำตอบและมักจะต้องเป็นการทำวิจัยแบบสหสถาบัน

ตามหลักการที่ถูกต้องนักวิชาการไม่สามารถเลือกผลงานวิจัยงานใดงานหนึ่งมาตอบคำถาม วิจัยนั้นๆ แต่ควรพิจารณาผลงานวิจัยที่มีคุณภาพดีที่เกี่ยวข้องกับเรื่องนั้น ๆ ทั้งหมด และนำเอา ข้อมูลมาสังเคราะห์รวมกันโดยใช้การวิจัยเชิงสังเคราะห์ (Research synthesis) ซึ่งประกอบด้วย ขั้นตอนที่สำคัญ 2 ขั้นตอนได้แก่ การทบทวนวรรณกรรมอย่างเป็นระบบ (systematic review) และ การวิเคราะห์ข้อมูลแบบ meta-analysis เป็นวิธีการที่ใช้สังเคราะห์งานวิจัยตั้งแต่ 2 งานวิจัยขึ้นไป เพื่อสรุปผลหาคำตอบสำหรับคำถามวิจัยแต่ละเรื่อง

ถึงแม้การวิจัยเชิงสังเคราะห์จะไม่ใช่วิธีใหม่แต่ยังมีนักวิชาการไม่มากนักที่เห็น ความสำคัญของการวิจัยแบบนี้ ในการวิจัยทางคลินิกการไม่ทำหรือไม่นำผลการวิจัยเชิงสังเคราะห์ มาใช้อาจจะทำให้เกิดผลเสียที่ร้ายแรงได้ ผู้ป่วยอาจเสียโอกาสที่จะได้รับการรักษาพยาบาลที่ ได้ผลดี หรืออาจจะได้รับการรักษาพยาบาลที่มีผลเสียมากกว่าผลดี อาจจะมีการทำวิจัยที่ไม่จำเป็น เพราะถ้าทำวิจัยเชิงสังเคราะห์โดยใช้งานวิจัยที่มีอยู่ก็จะได้คำตอบโดยไม่ต้องทำวิจัยแล้ว และทำให้ เกิดการใช้ทรัพยากรที่มีอยู่จำกัดอย่างไม่มีประสิทธิภาพ

ในปี พ.ศ. 2544 ได้มีการจัดตั้ง Thai Cochrane Network (TCN) โดยการสนับสนุนของ Department of Reproductive Health and Research, World Health Organization, The UK and Australian Cochrane Centres. TCN เป็นหน่วยงานแรกของ Cochrane Collaboration ในประเทศ ไทยและภูมิภาคเอเชียตะวันออกเฉียงใต้ วัตถุประสงค์ที่สำคัญของ TCN คือสนับสนุนให้มีการใช้ และการทำวิจัยเชิงสังเคราะห์กับ Cochrane Collaboration

2. วัตถุประสงค์

- 2.1 เพื่อผลิตนักวิจัยด้านวิทยาศาสตร์สุขภาพที่มีความสามารถทั้งด้าน clinical epidemiology research และ research synthesis
- 2.2 เพื่อผลิตงานวิจัยแบบนิพนธ์ต้นฉบับ (Original articles) เพื่อตีพิมพ์ในวารสารระดับนานาชาติ และงานวิจัยเชิงสังเคราะห์เพื่อตีพิมพ์ใน Cochrane Library และวารสารนานาชาติอื่น ๆ ตามความเหมาะสม
- 2.3 ดำเนินการให้มีการนำผลงานวิจัยไปใช้อย่างเป็นรูปธรรม

3. ระเบียบวิธีวิจัย

- 3.1 สำหรับการวิจัยแบบนิพนธ์ต้นฉบับ (Original articles) จะใช้ระเบียบวิธีวิจัยและวิธีการทางสถิติที่เหมาะสม
- 3.2 สำหรับการวิจัยเชิงสังเคราะห์จะใช้วิธีการและกลไกของ Cochrane Collaboration

4. ผลการดำเนินงานวิจัย (พ.ศ. 2550-2553)

- 4.1 มีนักวิจัยเข้าร่วมในโครงการจำนวน 43 คน จาก 11 สถาบัน
- 4.2 มีผลงานตีพิมพ์ใน international journals จำนวน 29 papers
 - 4.2.1 ตีพิมพ์ผลงานวิจัย Original articles และบทความใน international peer-reviewed journals จำนวน 17 เรื่อง
 - 4.2.2 ตีพิมพ์ผลงานวิจัยเชิงสังเคราะห์ (Cochrane reviews) ใน Cochrane Library จำนวน 12 เรื่อง
- 4.3 มีการตีพิมพ์ Protocols for Cochrane reviews ใน Cochrane Library จำนวน 9 เรื่อง

เนื้อหางานวิจัย

การวิจัยในโครงการประกอบด้วยส่วนสำคัญ 2 ส่วน ได้แก่

1. การวิจัยด้านระบาดวิทยาคลินิก (Clinical Epidemiology Research)

เป็นการดำเนินการวิจัยเพื่อตอบปัญหาที่เกี่ยวข้องกับการดูแลรักษาผู้ป่วยโดยใช้ระเบียบวิธีวิจัยและสถิติที่เหมาะสมได้แก่

1.1 Tranexamic acid for preventing progressive intracranial haemorrhage in adults with traumatic brain injury: A randomized, double-blinded, placebo controlled trial. (กำลังรอตีพิมพ์)

นอกจากนี้ยังมีงานวิจัยที่ใช้ข้อมูลจากโครงการที่ดำเนินมาก่อนหน้านี้และนำมาวิเคราะห์และตีพิมพ์ในวารสารนานาชาติ ได้แก่

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1.4 Pattanittum P, Ewens MR, **Laopaiboon M**, **Lumbiganon P**, McDonald SJ, Crowther CA, Study Group TS. Use of antenatal corticosteroids prior to preterm birth in four South East Asian countries within the SEA-ORCHID project. BMC Pregnancy Childbirth 2008; 16: 47.

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1.7 **Lumbiganon P**, Villar J, **Laopaiboon M**, Widmer M, **Thinkhamrop J**, Carroli G, Duc Vy N, Mignini L, Festin M, Prasertcharoensuk W, Limpongsanurak S, Liabsuetrakul T, Sirivatanapa P; World Health Organization Asymptomatic Bacteriuria Trial Group. One-day compared with 7-day nitrofurantoin for asymptomatic bacteriuria in pregnancy: a randomized controlled trial. *Obstet Gynecol* 2009; 113: 339-45.

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1.9 **Lumbiganon P**, **Laopaiboon M**, Gulmezoglu AM, Souza JP, Taneepanichskul S, Ruyan P, et al. Method of delivery and pregnancy outcomes in Asia: the WHO global survey on maternal and perinatal health 2007-08. *Lancet* 2010; 375: 490-9.

1.10 Chongsuvivatwong V, Bachtiar H, Chowdhury ME, Fernando S, Suwanrath C, Kor-Anantakul O, Tuan le A, Lim A, **Lumbiganon P**, Manandhar B, Muchtar M, Nahar L, Hieu NT, Fang PX, Prasertcharoensuk W, Radnaabarzar E, Sibuea D, Than KK, Tharnpaisan P, Thach TS, Rowe P. Maternal and fetal mortality and complications associated with cesarean section deliveries in teaching hospitals in Asia. *J Obstet Gynaecol Res* 2010; 36(1): 45-51.

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2. การวิจัยเชิงสังเคราะห์ (Research synthesis) สมาชิกของกลุ่มได้ร่วมทำการวิจัยเชิงสังเคราะห์ร่วมกับ Cochrane Collaboration ตามระเบียบวิธีวิจัยเชิงสังเคราะห์ที่เป็นมาตรฐานตามข้อกำหนดของ Cochrane review groups ต่าง ๆ ได้ดำเนินการวิจัยเรียบเรียงและตีพิมพ์ใน Cochrane Library แล้วจำนวน 12 เรื่อง ได้แก่

2.1 **Suwannachat B, Lumbiganon P, Laopaiboon M.** Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery. Cochrane Database Syst Rev 2008, Issue 3. Art. No.: CD006636.

2.2 **Thanaviratananich S, Laopaiboon M, Vatanasapt P.** Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media. Cochrane Database Syst Rev 2008, Issue 4. Art. No.: CD004975.

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2.5 **Srisubat A, Potisat S, Lojanapiwat B, Setthawong V, Laopaiboon M.** Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones. Cochrane Database Syst Rev 2009, Issue 4. Art. No.: CD007044.

2.6 **Boonmak P, Boonmak S.** Epidural blood patching for preventing and treating post-dural puncture headache. Cochrane Database Syst Rev 2010, Issue 1. Art. No.: CD001791.

2.7 **Perel P, Roberts I, Shakur H, Thinkhamrop B, Phuenpathom N, Yutthakasemsunt S.** Haemostatic drugs for traumatic brain injury. Cochrane Database Syst Rev 2010, Issue 1. Art. No.: CD007877.

2.8 **Ngamjarus C, Pattanittum P, Somboonporn C.** Roselle for hypertension in adults. Cochrane Database Syst Rev 2010, Issue 1. Art. No.: CD007894.

2.9 **Tangjitgamol S, Manusirivithaya S, Laopaiboon M, Lumbiganon P, Bryant A.** Interval debulking surgery for advanced epithelial ovarian cancer. Cochrane Database Syst Rev 2010, Issue 10. Art. No.: CD006014.

2.10 **Krisanaprakornkit T, Ngamjarus C, Witoonchart C, Piyavhatkul N.** Meditation therapies for attention-deficit/hyperactivity disorder (ADHD). Cochrane Database Syst Rev 2010, Issue 6. Art. No.: CD006507.

2.11 **Buppasiri P, Lumbiganon P, Thinkhamrop J, Thinkhamrop B.** Antibiotic prophylaxis for third- and fourth-degree perineal tear during vaginal birth. Cochrane Database Syst Rev 2010, Issue 11. Art. No.: CD005125.

2.12 **Siriwachirachai T, Sangkomkamhang US, Lumbiganon P, Laopaiboon M.** Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections. Cochrane Database Syst Rev 2010, Issue 12. Art. No.: CD007772.

3. ดำเนินการวิจัยเชิงสังเคราะห์ถึงขั้นตอนการตีพิมพ์ Protocol ใน Cochrane Library (เทียบได้กับจัดทำ Research proposal ที่ได้ผ่านการกลั่นกรองและรับรองจาก Cochrane Review Groups ต่าง ๆ แล้วและกำลังทำวิจัยเพื่อให้เป็น Cochrane reviews จำนวน 9 เรื่อง ได้แก่

3.1 **Buppasiri P, Lumbiganon P, Thinkhamrop J, Ngamjarus C.** Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes (Protocol). Cochrane Database Syst Rev 2008, Issue 2. Art. No.: CD007079.

3.2 **Muktabhant B, Lumbiganon P, Ngamjarus C.** Interventions for preventing excessive weight gain during pregnancy (Protocol). Cochrane Database of Syst Rev 2008, Issue 2. Art. No.: CD007145.

3.3 **Khianman B, Pattanittum P, Thinkhamrop J, Lumbiganon P.** Relaxation therapy for preventing and treating preterm labour (Protocol). Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD007426.

3.4 **Khanprakob T, Laopaiboon M, Lumbiganon P, Sangkomkamhang US.** Cyclo-oxygenase (COX) inhibitors for preventing preterm labour (Protocol). Cochrane Database Syst Rev 2009, Issue 2. Art. No.: CD007748.

3.5 **Sangkomkamhang US, Lumbiganon P, Laopaiboon M.** Hepatitis B vaccination during pregnancy for preventing infant infection. Cochrane Database Syst Rev 2009, Issue 3. Art. No.: CD007879.

3.6 **Piromchai P, Thanaviratananich S, Laopaiboon M.** Antibiotics for chronic rhinosinusitis in adults (Protocol). Cochrane Database Syst Rev 2010, Issue 1. Art. No.: CD008233.

3.7 **Sangkomkamhang T, Sangkomkamhang US, Ngamjarus C.** Vitamin K for the prevention and treatment of osteoporosis in post-menopausal women (Protocol). Cochrane Database Syst Rev 2010, Issue 1. Art. No.: CD008329.

3.8 **Khunpradit S, Lumbiganon P, Laopaiboon M.** Admission tests other than cardiotocography for fetal assessment during labour (Protocol). Cochrane Database Syst Rev 2010, Issue 3. Art. No.: CD008410.

3.9 **Tiamklang T, Sumanont S, Foocharoen T, Laopaiboon M.** Double-bundle versus single-bundle reconstruction for anterior cruciate ligament rupture in adults (Protocol). Cochrane Database Syst Rev 2010, Issue 3. Art. No.: CD008413.

Outputs ที่ได้จากโครงการ (2550-2553)

1. ตีพิมพ์ผลงานวิจัย Original articles และบทความใน international peer-reviewed journals จำนวน 17 เรื่อง (กรณาดูรายละเอียดในภาคผนวกที่ 1)
2. ตีพิมพ์ผลงานวิจัยเชิงสังเคราะห์ (Cochrane reviews) ใน Cochrane Library จำนวน 12 เรื่อง (กรณาดูรายละเอียดในภาคผนวกที่ 2)
3. มีนักวิจัยเข้าร่วมในโครงการจำนวน 43 คน จาก 11 สถาบัน (กรณาดูรายละเอียดในภาคผนวกที่ 3)
4. ประเทศไทยมีโครงการวิจัยเชิงสังเคราะห์ที่ทำร่วมกับ Cochrane Collaboration มากขึ้นอย่างรวดเร็วและปัจจุบันเป็นอันดับที่ 3 ใน Asia รองจากจีน และอินเดียเท่านั้น (กรณาดูเอกสารในภาคผนวกที่ 4)
5. ตีพิมพ์ Protocols for Cochrane reviews ใน Cochrane Library จำนวน 9 เรื่อง (กรณาดูรายละเอียดในภาคผนวกที่ 5)
6. งานวิจัยที่ได้ตีพิมพ์ใน international peer-review journals และ Cochrane Library ได้นำไปอ้างอิงในวารสารต่างประเทศ จำนวน 57 ครั้ง (กรณาดูรายละเอียดในภาคผนวกที่ 6)
7. เรียบเรียงหนังสือ การวิจัยเชิงสังเคราะห์ในการดูแลรักษาสุขภาพ (Research Synthesis in Healthcare) จัดพิมพ์เผยแพร่ไปตามห้องสมุดคณะแพทยศาสตร์ทุกแห่ง คณะสาธารณสุขศาสตร์ทุกแห่ง และโรงพยาบาลทั่วไปของกระทรวงสาธารณสุขทุกแห่ง และได้นำขึ้นเว็บไซต์ Thai Cochrane Network ที่ <http://tcn.cochrane.org/recent-update>

ภาคผนวกที่ 1

ตีพิมพ์ผลงานวิจัย Original articles และบทความใน
international peer-reviewed journals จำนวน 17 เรื่อง

Improving the reporting of public health intervention research: advancing TREND and CONSORT

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ABSTRACT

Background Evidence-based public health decision-making depends on high quality and transparent accounts of what interventions are effective, for whom, how and at what cost. Improving the quality of reporting of randomized and non-randomized study designs through the CONSORT and TREND statements has had a marked impact on the quality of study designs. However, public health users of systematic reviews have been concerned with the paucity of synthesized information on context, development and rationale, implementation processes and sustainability factors.

Methods This paper examines the existing reporting frameworks for research against information sought by users of systematic reviews of public health interventions and suggests additional items that should be considered in future recommendations on the reporting of public health interventions.

Results Intervention model, theoretical and ethical considerations, study design choice, integrity of intervention/process evaluation, context, differential effects and inequalities and sustainability are often overlooked in reports of public health interventions.

Conclusion Population health policy makers need synthesized, detailed and high quality *a priori* accounts of effective interventions in order to make better progress in tackling population morbidities and inequalities. Adding simple criteria to reporting standards will significantly improve the quality and usefulness of published evidence and increase its impact on public health program planning.

Keywords public health, primary research, evidence, editorial policies

Introduction

For many years, primary research has been supported by statements or guidelines aimed at improving the quality of reporting. This has resulted in significant improvements in reports of intervention studies, particularly for clinical randomized controlled trials (RCTs). However, there remain many deficiencies in these frameworks for the reporting of complex public health interventions. This has implications for those who conduct systematic reviews of public health interventions, those who conduct implementation evaluations or health systems research and those who use these forms of evidence to inform their decision-making. This paper examines the existing reporting frameworks against information sought by users of systematic reviews of public health interventions, and suggests key additional items that

should be considered in future recommendations on the reporting of public health interventions by researchers and publishers. As the demand for high quality, transparent secondary research increases amongst health care policy makers

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and other end-users it is an auspicious time to address these issues.^{1–3}

Value of CONSORT and TREND in improving the reporting of primary research

The Consolidated Standards of Reporting Trials (CONSORT) statement was first developed in 1996 (and updated in 2001)^{4,5} with the aim of improving the quality of reporting of RCTs. It requires authors of reports and journal articles to follow a checklist of 22 items that should be reported. CONSORT has now been adopted by more than 150 medical, clinical and psychological journals (www.consort-statement.org). The need for an alternate statement to improve the reporting of non-randomized studies was subsequently identified in 2004. This resulted in the development of the Transparent Reporting of Evaluations with Non-randomized Designs (TREND) Statement.⁶ The TREND statement is potentially very important for disciplines such as public health where debate continues about the extent to which RCTs are feasible or appropriate.^{7,8}

A number of other guidelines have also been published to support the systematic review process including QUORUM⁹ (recently renamed PRISMA) (reporting systematic reviews of RCTs), STROBE¹⁰ (reporting of observational studies) and MOOSE¹¹ (reporting systematic reviews of observational studies). The National Knowledge Service in the UK has funded EQUATOR which will act as an umbrella organization to coordinate work with the mutual interest of 'improving the quality of research publications and of research itself'.¹²

CONSORT and TREND were primarily conceived to increase the ability of research consumers to judge the internal validity of published studies, and thereby gain an appreciation of potential sources of bias that may have had some influence on the trial result. Key threats to internal validity that were often hidden in reports of trials were subversion of randomization, blinding and response bias, which are each covered by items in CONSORT. The statement has been associated with improvements in the quality of reporting of primary research: a systematic review conducted in 2006 found that journals using CONSORT had significantly better reporting of method of sequence generation (risk ratio [RR], 1.67; 95% CI, 1.19–2.33), allocation concealment (RR, 1.66; 95% CI, 1.37–2.00) and overall number of CONSORT items than those not using CONSORT (standardized mean difference, 0.83; 95% CI, 0.46–1.19).¹³ CONSORT appeared to have had less effect on items including reporting of participant flow, and blinding of participants or data analysts.¹³ Where studies

compared journals pre- and post-adoption of CONSORT an improvement was found in the description of the method of sequence generation (RR, 2.78; 95% CI, 1.78–4.33), participant flow (RR, 8.06; 95% CI, 4.10–15.83) and total CONSORT items (standardized mean difference, 3.67 items; 95% CI, 2.09–5.25) all improved after the adoption of CONSORT.¹³ This review is currently being updated.¹⁴

However, CONSORT was less concerned with other aspects of the conduct and reporting of intervention studies which can be equally critical to maximize the appropriateness of inferences to be drawn from such research. Within the context of randomized trials of drugs and other well-defined interventions, concerns regarding pre-specification of primary outcomes and planned sub-group analyses have been better addressed through the publication and registration of trial protocols. In the context of more complex interventions, where key concerns are to unpack the 'black box' of the intervention¹⁵ and to make clear assessments about the external validity of the study¹⁶ challenges remain in the reporting of randomized and non-randomized trials and therefore in the interpretation and synthesis of the evidence they provide.

Further, unlike the CONSORT statement which has seen widespread support, the TREND statement appears to be only formally supported by 15 journals. These are primarily in areas of HIV/AIDS, behavioural medicine or psychology, but supporters also include the BMJ and the American Journal of Public Health, which published the statement. It is not known whether other journals informally support TREND or why the uptake has been slower than for CONSORT.

Reporting frameworks can guide primary public health research

Although statements such as CONSORT and TREND have been established to improve the reporting of research, they have also provided researchers with a framework by which to design the primary research itself. Relevant items relate primarily to the mechanics of the scientific conduct of the study; what was implemented and what results occurred and how might these be interpreted. However, although CONSORT and TREND have usefully outlined the key methodological components of randomized and non-randomized trials that need to be reported, additional information is required by users of research to determine generalizability, applicability and transferability. Public health interventions are inherently complex and as such the interpretation of findings is frequently dependent on a range of contextual factors, irrespective of the study design.

The authors of the TREND statement have encouraged feedback on their work and some useful ideas have been subsequently published: Dziewaltowski *et al.*¹⁷ have suggested an increase in focus on factors that impact on external validity. This would include a particular focus on the impact of setting-level factors and intervention staff, skills, intervention costs and long-term outcomes that provide information on whether effects are sustained. Kirkwood⁸ has suggested the authors reflect on the applicability of the items that are based heavily on those outlined in CONSORT and suggests additional guidance for development of interventions, process and confounding variables and evaluation design. Further, one obviously useful modification to the TREND statement, in order to increase its usability by public health, health promotion, practitioners and researchers, would be to expand its focus beyond HIV/AIDS.

In 2001, core information needs required of systematic reviews of public health interventions for public health decision-making were described^{18,19} by users of evidence within global public health policy and programs. The subsequent application of these guidelines in systematic reviews of public health interventions has demonstrated that many sought after dimensions have not been included in either the conduct or reporting of the primary research studies.²⁰ These dimensions have been mapped against the key criteria of CONSORT and TREND to identify the missing components in the existing statements, and used to formulate the suggestions outlined below that are presented in order of the paper section in which they should be reported.

Reporting INTRODUCTION/BACKGROUND

Intervention model and theoretical considerations

Far too often, public health interventions are tested for effectiveness without such a model being established and/or reported, and this leads to poorly specified systematic reviews in which substantially different interventions are lumped together due to similarities in key superficial aspects such as intervention form, setting and/or target health behaviour.¹⁹ Thus, for example, it has been concluded that school based smoking education is ineffective²¹ and should be abandoned, even though there are promising approaches which need to be identified, developed and evaluated.²²

Another area of research where interventions are often complex is health services research, where integrated care pathways can be broken down into critical components.²³ Public health intervention research needs to identify similar ways of describing the intervention-process-outcome

pathway. It is important to have a clear model which sets out how the intervention is intended to bring about change in the intended outcomes, and reports of public health intervention studies should publish such a model as a requirement to allow intelligent consumption and synthesis. In the evaluation field this is known as the logic model.^{24,25} Ideally, the model should distinguish core and peripheral components, and emphasize the relative importance of form and function²⁶ so that the essence of the intervention is captured allowing the integrity of the intervention to be maintained in future implementation.

This section should also provide some detail on the development and piloting of the intervention, and present any theoretical or empirical support for the intervention model and the way it is being operationalized in the intervention. There should also be discussion of potential negative outcomes of the intervention (including the timing and measurement used to assess them²⁷), and any particular ethical concerns that there might be.²⁸

Reporting METHODS

Study design choice

Authors should justify the choice of study design, particularly where the chosen design has been reached as a compromise between the requirements of research rigour and internal validity on the one hand, and the complexity and constraints of the research question and research setting on the other. It may be possible to identify a consistent way of identifying key strengths and weaknesses of the chosen study design, relating particularly to internal validity issues and of describing the justification for accepting design limitations. Key components of study design that should be justified are the research design, operationalization of the design including group allocation and choice of counterfactual, choice of outcome measures and measurement methods.

Reporting RESULTS

Integrity of intervention/process evaluation

The integrity (or fidelity) of the intervention is the degree to which the intervention is implemented as planned.²⁸ Dane and Schneider²⁹ identify aspects of integrity/fidelity as adherence, exposure, quality of delivery, participant responsiveness and program differentiation. All five dimensions should be measured in order to provide a comprehensive picture of intervention integrity.²⁹ CONSORT does not explicitly mention fidelity and while the TREND statement recommends including issues of fidelity in the interpretation

of results, an additional guidance is required to describe how this should be achieved. This is particularly important given that only a limited number of studies disentangle the factors that ensure successful outcomes, characterize the failure to achieve success or attempt to document the steps involved in achieving successful implementation of complex interventions.^{30,31} Process evaluations provide a mechanism to collect and report on intervention fidelity^{15,28} and when reported should include information on the intensity, duration and reach of intervention components, and how these varied by sub-group. Increased access to existing checklists and resources that support the reporting of process evaluations would be beneficial.

Context, differential effects and multi-level processes

The success or failure of a complex public health intervention is often highly dependent on the social, economic and political context in which it is developed and operated.³² Knowing this type of information provides important clues about the applicability and transferability of interventions to other populations or organizational contexts. It also helps to highlight the critical success factors and the elements that are more likely to lead to program failure. Hawe³³ has outlined a range of important contextual information: aspects of the host organization and staff, aspects of the system, characteristics of the target population and inter-organizational networks. These factors should be considered in reporting of public health interventions. Although these data are often collected, they are often then excluded from publications. It would be useful to highlight within publications where this information has been collected but not reported by referring readers to a website or full report.

It is well established through perspectives such as McLeroy's socio-ecological model framework³⁴ and the WHO Ottawa Charter³⁵ that interventions do not work in isolation and require multi-level processes. Effectiveness will vary importantly with reference to context: what works in one setting or population group would not necessarily work in another.^{32,36} Thus reports need to include a description of multi-level processes and a strong set of data to contextualize the study (external validity). They should also report sub-group effects by key demographic and policy factors such as SES, ethnicity and gender so that pooled analysis can be done without needing to obtain original datasets. Counter to established orthodoxy in the analysis and reporting of effectiveness trials, there may be some value in undertaking and reporting sub-group analyses even where there is insufficient statistical power within the study. This would allow pooled analysis of

these sub-group effects to be undertaken in systematic reviews. This is particularly important in considering the differential effect of interventions by socio-economic status to assess the magnitude and direction of the effects of an intervention on health inequalities.^{37,38} Neither CONSORT nor TREND specifically address issues pertaining to inequalities.

Sustainability

Effective public health programs or interventions should attempt to assess the degree to which they would be sustainable beyond the life of the program. In acknowledging this, it is also important to highlight that assessing the sustainability of a program and or its effects is an additional research question requiring supplementary research design development and study conduct. Shediach-Rizkallah and Bone³⁹ present a useful framework to address sustainability. In this framework, the key aspects of program sustainability are defined as maintenance of health benefits from the program, institutionalization of a program within an organization and capacity building in the community. In reporting, authors should consider the economic and political variables, the strength of the organization, the degree to which activities are integrated into existing programs and policies and the degree of community involvement/participation.⁴⁰

Reporting DISCUSSION

Many of the sections above make recommendations for reporting complex public health interventions that should also be considered in the discussion section. We would highlight specifically the opportunity that this section provides for authors to fully discuss limitations of study design and honestly appraise weaknesses. It also allows authors to interpret and discuss any sub-group effects or interactions with context that seem important. As a conclusion to the report, authors should reflect on the original model used and make statements about what worked well and what not so well so that future research or implementation can learn and further develop. An important aspect of this model could include unanticipated effects of the intervention that the investigators became aware of during the course of the study.⁴¹ Although such effects cannot be interpreted in the same way as those outcomes hypothesized and planned for in study design, they are frequently important both for future intervention development and also for the planning of future evaluation studies to capture wider potential harms and benefits, and more broadly scope the potential intervention effects.^{27,42}

Can it possibly fit in journal word limits?

A strength of CONSORT is that it identifies the key elements required in reports of RCTs and as such has assisted authors in producing concise papers that meet the increasingly tight word length requirements of journals.¹⁴ A potential problem for the inclusion of the additional items suggested above is that it will be impossible to adequately report these items without substantial additional text, which traditional printed journals may find difficult to accommodate. Further work will be required to identify efficient, elegant and concise ways of presenting the additional data required, which may, for example, include diagrams of the hypothesized pathway from intervention to intended outcome, or describing the intervention components in a separate text box which does not contribute to overall word length.

Other possibilities may be that online editions of journals offer more space or act as channels to publish supporting documentation covering details of the suggested items. Or more radically, in parallel with established practice in clinical research, there needs to be increased funding and more opportunities for publication of intervention development research, covering phases 1–3 of the MRC Framework⁴³ such that this work is peer-reviewed and published as a precursor to large scale effectiveness studies.

Conclusion

Guidelines for the reporting of public health intervention research are not currently available to the extent to which they are required. Given the need to increasingly understand *what works, for whom, why, when and at what cost*, standards for reporting on public health interventions, aligned with registries and evaluation frameworks,⁴⁴ have the potential to make a significant impact on the capacity to better understand these dimensions for the benefit of public health policy.

The CONSORT and TREND statements have been important in improving the quality of published RCTs and non-randomized evaluations of interventions. This paper has suggested key elements which are additionally needed in the reporting of complex public health interventions. It is hoped that further development of these suggestions will lead to improved conduct and reporting of primary intervention studies, enrichment of systematic reviews of public health interventions and therefore greater support for informed decision-making.

Development of comprehensive guidelines will require the establishment of an international taskforce. A range of practitioners, policy-makers and researchers across different countries and organizational contexts will need to be

members of this taskforce. This will ensure that the guidelines and recommendations meet the needs of public health researchers, practitioners and funders more broadly. If we are to 'improve the quality of research publications and of research itself',¹² then this is a necessary step forward.

New public health relevant Cochrane reviews and protocols from issues 3 and 4, 2007

Reviews

- Abstinence-only programs for HIV infection prevention in high-income countries.
- Diet or exercise, or both, for weight reduction in women after childbirth.
- Home-based support for disadvantaged adult mothers.
- Home-based support for disadvantaged teenage mothers.
- Exercise for improving balance in older people.
- Interventions for the prevention of nutritional rickets in term born children.
- Interventions in the workplace to support breastfeeding for women in employment.
- Interventions to reduce harm from continued tobacco use.
- Parenting interventions for the prevention of unintentional injuries in childhood.
- School-based education programs for the prevention of child sexual abuse.
- Traditional birth attendant training for improving health behaviours and pregnancy outcomes.

Protocols

- Dietary advice in pregnancy for preventing gestational diabetes mellitus.
- Harm reduction interventions to prevent HIV/AIDS transmission in involuntary detainees.
- Indoor residual spraying for preventing malaria.
- Maternity waiting facilities for improving maternal and neonatal outcome in low-resource countries.
- Mobile phone-based interventions for smoking cessation.
- Routine iron supplementation for preventing or treating iron-deficiency anaemia in children in malaria-endemic areas.
- Routine vs. voluntary HIV testing for increasing HIV testing rates.
- Salt fluoridation for preventing dental caries.
- Social norms interventions to reduce alcohol misuse in University or College students.
- Vitamin C for preventing and treating tetanus.
- Zinc supplements for preventing otitis media.

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Reporting the findings of clinical trials: a discussion paper

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Background

When researchers embark on a clinical trial, they make a commitment to conduct the trial and to report the findings in accordance with basic ethical principles. This includes preserving the accuracy of the results and making both positive and negative results publicly available.¹ However, a significant proportion of health-care research remains unpublished and, even when it is published, some researchers do not make all of their results available.² Selective reporting, regardless of the reason for it, leads to an incomplete and potentially biased view of a trial and its results.³

The consequences of publication bias and selective reporting have gained the attention of health-care consumers, the media and politicians. All have recognized the impact that undisclosed results can have on the ability of patients, practitioners and policy-makers to make well-informed decisions about health care. Concern over the underreporting of adverse events, in particular, has increased the demand for more transparent processes for registering clinical trials and reporting their findings. In recent years, trial registration has become increasingly widely accepted and implemented. There are now well-established mechanisms to register trials, assign unique identifiers and make this information publicly available. WHO's International Clinical Trials Registry Platform Search Portal helps bring the data from these registers together, making it much easier to search for the existence of a trial

(available at: <http://www.who.int/trialsearch>).

The value of registration goes far beyond the administrative benefits of having a complete collection of all trials. Trial registers may facilitate recruitment into clinical trials by raising awareness of their existence among potential participants and health-care practitioners. They may also lead to more ethical and successful research by avoiding the unintentional duplication of research already under way elsewhere. From the perspective of this paper, however, the greatest benefit of trial registration is enhanced transparency; that is, making it clear which trials are being conducted so that people can anticipate their results.

The next step to informed decision-making is to make the findings of clinical trials available, since it is knowledge of the findings, rather than of the existence of a trial, that is likely to have the greatest impact on people trying to choose between alternative interventions. The arrival and growth of electronic publishing and the Internet as dissemination tools without page or length restrictions has greatly expanded the ability of people to make findings available and accessible in full. The recognition of the need for reliable evidence to improve health care and to facilitate the synthesis of the results of research into systematic reviews has fuelled the demand for access to the findings of all research, as have the needs of the numerous other stakeholders in clinical research.

A proposed position

The position proposed by the members of the WHO Registry Platform Working Group on the Reporting of Findings of Clinical Trials is that "the findings of all clinical trials must be made publicly available". This paper discusses the principles underlying this position. Our goal is to contribute to the ongoing debate and to foster the collaboration that is necessary to ensure that the findings of clinical trials do not remain hidden from the people who need access to them.

What is a finding?

The language used to discuss the reporting of clinical trials usually focuses on "results" – often taken to mean the numerical results of an analysis for a specific outcome. For example, a summary estimate such as a relative risk. However, the reader or user of research also needs background information that will allow them to correctly interpret the results for specific outcomes. The type and amount of information required will depend on the nature of the audience and how it will use the information received but will have four key elements:

1. Methodological context

The user needs to know what the original plans for the trial were and how it was actually conducted. Some of the original plans will be available if the trial was registered, but more complete

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information should be in the full trial protocol. The actual conduct of the trial might, however, differ from that planned. Such differences may be valid but should be traceable, preferably via a clinical trial registry. The methodological context for a trial might also include information on the primary question that the researchers set out to answer; the hypothesis they were seeking to test; the methods they used to allocate or select participants for the interventions; whether any blinding or masking was done; and a description of the statistical methods planned and used, including a justification of the sample size.

2. Population context

The user needs to consider to whom the results of the trial can be applied. They need to know the characteristics of the population it was initially intended to recruit, as well as the characteristics of the population who were recruited. In reporting their findings, the researchers should therefore refer to the original inclusion and exclusion criteria and provide information on the population that actually took part, describing the extent to which participants left the trial early (with reasons for doing so) and whether interventions were delivered as planned.

3. A result for each outcome

A clinical trial will usually consider several outcomes, each of which might be measured in multiple ways or at multiple time points, and there might be more than one way to analyse each of these measures. The findings should contain the results for every outcome measure and analysis specified in the register entry for the trial, and set out in the protocol or statistical analysis plan. If any of these results are not reported, a reason should be provided for their absence. Any findings from analyses that were not pre-specified should be clearly identified as such.

4. Interpretation

The most contentious aspect of reporting the findings of a clinical trial may be whether the report should include the researchers' opinions and conclusions. It is in this section of a report where the objectivity of the research is confronted by the subjectivity of authors who "use their power as owners of their writing to emphasize one point of view more than another".⁴ Alternatively, linguistic spin is considered by some to be essential to scientific communication, being the opportunity for scientists to speculate and formulate new hypotheses.⁵ Distinguishing opinions and conclusions from advocacy or promotion can be difficult, and it may be preferable to leave the users of the findings to draw their own conclusions and form their own opinions of what the findings of a trial mean for them and their decision-making.

Public availability

Clinical trial results should be available to everyone, regardless of where they live. If the results are not made available within a reasonable period, the reasons for delay and a date by which the findings will be available should be submitted to the relevant clinical trials registry. It should be the responsibility of researchers to produce their findings in a format that can be accessed by potential users, and it should be the responsibility of the user to seek these results. The Internet could provide the main means by which this shared responsibility can be satisfied. Access also needs to be considered in terms of the end user's ability to both view and understand the information obtained.

Historically, access to the results of a trial has usually been achieved through publication in a peer-reviewed journal. This traditional publication model has its limitations, particularly

in an environment where the end users of research information now include health-care policy-makers, consumers, regulators and legislators who want rapid access to high quality information in a "user-friendly" format. In future, researchers may be legally required to make their findings publicly available within a specific timeframe (assuming any legislation created does not have escape clauses built in). In the United States of America, such legislation is already in place (available at: <http://www.fda.gov/oc/initiatives/HR3580.pdf>). This may compromise the ability of researchers to publish trial findings in a peer-reviewed journal. Although some journal editors have acknowledged the changing climate around results registration and reporting (available at: http://www.icmje.org/clin_trial07.pdf), they may have a conflict of interest in that they will probably want the key (and potentially most exciting) messages from a trial to appear first, and perhaps exclusively, in their publication.

Conclusion

People making decisions about health care need access to knowledge derived from the findings of clinical trial research. Following on from WHO's position that all clinical trials must be registered,⁶ it is proposed that the findings of all clinical trials must be made publicly available. This report is the start of a consultation process on how this goal of transparency can be achieved, with the intention that greater accessibility to the findings of all clinical trials will lead to improvements in health and health care. To contribute to the first phase of the consultation, please visit: <http://www.who.int/ictrp/results/consultation> ■

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Use of Evidence-Based Practices in Pregnancy and Childbirth: South East Asia Optimising Reproductive and Child Health in Developing Countries Project

The SEA-ORCHID Study Group*

Abstract

Background: The burden of mortality and morbidity related to pregnancy and childbirth remains concentrated in developing countries. SEA-ORCHID (South East Asia Optimising Reproductive and Child Health In Developing countries) is evaluating whether a multifaceted intervention to strengthen capacity for research synthesis, evidence-based care and knowledge implementation improves adoption of best clinical practice recommendations leading to better health for mothers and babies. In this study we assessed current practices in perinatal health care in four South East Asian countries and determined whether they were aligned with best practice recommendations.

Methodology/Principal Findings: We completed an audit of 9550 medical records of women and their 9665 infants at nine hospitals; two in each of Indonesia, Malaysia and The Philippines, and three in Thailand between January–December 2005. We compared actual clinical practices with best practice recommendations selected from the Cochrane Library and the World Health Organization Reproductive Health Library. Evidence-based components of the active management of the third stage of labour and appropriately treating eclampsia with magnesium sulphate were universally practiced in all hospitals. Appropriate antibiotic prophylaxis for caesarean section, a beneficial form of care, was practiced in less than 5% of cases in most hospitals. Use of the unnecessary practices of enema in labour ranged from 1% to 61% and rates of episiotomy for vaginal birth ranged from 31% to 95%. Other appropriate practices were commonly performed to varying degrees between countries and also between hospitals within the same country.

Conclusions/Significance: Whilst some perinatal health care practices audited were consistent with best available evidence, several were not. We conclude that recording of clinical practices should be an essential step to improve quality of care. Based on these findings, the SEA-ORCHID project team has been developing and implementing interventions aimed at increasing compliance with evidence-based clinical practice recommendations to improve perinatal practice in South East Asia.

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Introduction

The burden of mortality and morbidity related to pregnancy and childbirth remains concentrated in developing countries [1,2]. This disparity continues with rates of neonatal mortality almost 10 times greater in South East Asia than developed regions [3,4]. SEA-ORCHID, a five-year project, is evaluating whether a multifaceted intervention to strengthen capacity for research synthesis, evidence-based care and knowledge implementation improves adoption of best clinical practice recommendations and so leads to better health for mothers and babies [5]. This paper describes empirical evidence of current practices at the beginning of the SEA-ORCHID project for key aspects of maternal and perinatal health care in the participating countries.

Methods

Setting

This audit was conducted in nine hospitals across Indonesia, Malaysia, The Philippines and Thailand, with support from three sites in Australia. Different types of hospital were represented including tertiary referral hospitals (University and regional), provincial hospitals and district hospitals. All were selected as part of the SEA-ORCHID project.

Seven of the hospitals were tertiary referral institutions with regional referrals of women with a high risk pregnancy. Two hospitals were provincial or district institutions. Models of delivery care included a multidisciplinary approach with midwives (including nurses with midwifery qualifications) or obstetric specialists. All hospitals had obstetric specialists and caesarean

section facilities available. Normal vaginal births were conducted by doctors and/or midwives (including nurses with midwifery qualifications) in all hospitals.

The SEA-ORCHID project settings and methods have been published elsewhere. [5]. The project was approved by the local ethics committee of each hospital and by the ethics committee of the administering institution in Australia (University of Sydney).

Procedure

We reviewed the medical records of 9550 women (9665 infants including 111 twins and two sets of triplets) admitted to the labour wards at the nine study hospitals between January–December 2005. The duration of data collection varied according to the number of births per month at the participating hospital. Five hospitals in the sample collected data on a consecutive basis until reaching a total of at least 1000 women. To avoid potential biases associated with short data collection periods, the four largest hospitals sampled cases using various ratios to ensure there was at least a three-month minimum data collection period at each hospital.

Staff at each hospital were trained to prospectively audit medical records using pre-established data extraction forms. We extracted information about current maternal and perinatal practice according to beneficial forms of care and forms of care likely to be ineffective or harmful as suggested in the World Health Organization Reproductive Health Library No.7 [6] and the Cochrane Library [7] (Table 1). The primary caregiver at the birth provided details of the presence of maternal companionship during the labour.

In addition we collected information on maternal characteristics including age, parity, height and weight, and on birth outcomes including gestational age at birth, mode of birth, birth weight, Apgar scores and perinatal mortality.

Completed data extraction forms were sent from the hospitals to the project co-ordinating site in each country for manual data entry by the trained fieldworkers using a secure web-based database. The online form was set-up to minimise transcription errors by performing validation checks to detect discrepancies and missing data. A random sample of between 5 to 10% was independently checked by project staff at one of the Australian support sites to identify data processing errors.

Data analysis

Descriptive analyses were performed across countries and between hospitals within countries. We used STATA software version 8.0 for data analysis [8]. We used frequencies to describe maternal characteristics, maternal and perinatal practices, as well as birth outcomes measured as categorical data. We used means and standard deviations to describe the continuous data variables of maternal age and gestational age at birth.

Results

Maternal characteristics and birth outcomes (Table 2)

For the 9550 mothers (and their 9665 babies) across the nine hospitals in South East Asia, the mean age per hospital ranged from 26 to 31 years. The rate of nulliparity varied, being over 40% in all hospitals of Indonesia, The Philippines and Thailand, and up to 64% in one Thai hospital but only 27% for one Malaysian hospital.

For the 9665 babies, the preterm birth rate (<37 weeks gestation) ranged from 6% to 15%. Overall 30% of all babies were born by caesarean section but the rate varied considerably across the nine hospitals ranging from 12% to 39%. Around a fifth of babies were born by caesarean section in the Malaysian hospitals and over a third in the Thai hospitals. Overall, 18% of babies were of low birth weight (<2500g) with rates ranging from 9% to 20%.

Table 1. Recommended practices in maternal and perinatal health care

Recommended practice	Care practices assessed	Outcome intended to reduce
Beneficial forms of care		
Antibiotics for preterm prelabour rupture of membranes (pPROM) [15]	Use of antibiotics in women with preterm (<37 weeks) prelabour rupture of membranes	Chorioamnionitis; neonatal sepsis
Corticosteroids prior to preterm birth [16]	Use of antenatal corticosteroids in women at risk of preterm birth at <34 weeks gestation	Neonatal death; complications of preterm birth
Continuous support during labour [17]	Family member present with the woman during childbirth	Caesarean section rate
Magnesium sulphate for eclampsia and pre-eclampsia [18,19,20]	Use of magnesium sulphate for women with eclampsia and pre-eclampsia	Maternal death; eclampsia
Management of third stage of labour [21]	Use of uterotonic and controlled cord traction in the third stage of labour	Postpartum haemorrhage; maternal death
- appropriate administration of a prophylactic oxytocic at or after birth of the baby		
- controlled umbilical cord traction to deliver the placenta		
Intraoperative antibiotics during caesarean section [14]	Administration of a single dose of ampicillin or first generation cephalosporin after umbilical cord clamping at caesarean section	Maternal infection
Immunisation for Hepatitis B [22]	Vaccination of babies against Hepatitis B virus	Hepatitis B infection
Forms of care likely to be unnecessary or harmful		
Routine episiotomy [23]	Restrictive use of episiotomy	Perineal injury; maternal infection
Routine shaving* [24]	Avoidance of pubic hair shaving	Maternal infection
Routine enemas* [25]	Avoidance of use of enemas during labour	Maternal infection

*No clear evidence from Cochrane reviews to support or refute use, but identified as practices of importance to research and evaluate
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Table 2. Percent distribution of maternal and infant outcomes across nine hospitals in South East Asia

Countries	Indonesia				Malaysia				The Philippines				Thailand			
	Hospitals	Overall	Tertiary	District	Overall	Overall	Tertiary 1	Tertiary 2	Overall	Tertiary 1	Tertiary 2	Overall	Regional	University	Provincial	
Mothers*		2086	1019	1067	2379	2379	1249	1130	2085	1026	1059	3000	1000	1000	1000	
Infants*		2113	1028	1085	2410	2410	1267	1143	2098	1026	1072	3044	1019	1013	1012	
Maternal age (years) ^c		30 (5.9)	30 (6.0)	30 (5.7)	30 (6.5)	30 (6.5)	29 (6.4)	31 (6.5)	27 (6.6)	26 (6.4)	28 (6.8)	27 (6.1)	26 (6.2)	28 (5.6)	27 (6.3)	
Nulliparous [†]		46	46	46	31	31	36	27	48	55	41	58	64	54	58	
Preterm birth (gestation <37 weeks) [†]		10	14	6	10	10	10	10	7	6	9	11	15	10	8	
Caesarean section [†]		30	29	31	19	19	22	17	23	12	33	35	34	34	39	
Low birth weight [†] (<2500 gm)		18	20	16	11	11	11	11	20	19	20	11	15	9	10	
APGAR Scores <7 at 5 minutes [†]		8	10	6	1	1	1	1	1	1	2	2	2	2	2	
Perinatal death* Per 1000 total births		35	42	29	12	12	11	12	4	5	3	16	15	21	13	

Figures are number* and mean (standard deviation)^a or percentage[†] (rounded to the nearest whole number)
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Rates of babies with Apgar scores less than seven at five minutes and perinatal death were highest in the two Indonesian hospitals, compared with rates in the other hospitals. Stillbirths accounted for more than 60% of the perinatal deaths in most hospitals across the countries. There were no maternal deaths prior to discharge reported in any of the hospitals during the audit.

The variation in rates between countries and between hospitals within the same country are likely to be influenced by the sociodemographics and risk status of the populations they care for, and the type of hospital (tertiary, provincial or district).

Beneficial forms of care

The recommended beneficial clinical practices were classified according to periods of pregnancy care: antenatal, intrapartum and postpartum (Table 3). The use of these clinical practices varied markedly across the nine hospitals.

Care practices during the antenatal period to treat pregnancy complications (Table 3). Women with pre-eclampsia represented 4% of the sample; with nearly three-quarters of the women with pre-eclampsia receiving magnesium sulphate. The rate of practice of this intervention varied among the hospitals within Malaysia (range 13% to 44%) and Thailand (range 57% to 82%) but was 100% in both Indonesian hospitals. There were 15 (0.16%) cases of eclampsia. Magnesium sulphate was used in all 15 (100%) of these cases of eclampsia, and in all countries involved in the audit.

Women with preterm prelabour rupture of the membranes (pPROM) received antibiotics 80% of the time. Although this practice was observed in all hospitals, the rates of administration varied across countries (range 62% to 92%) and hospitals (range 44% to 100%). In Indonesia, use was appropriately high whereas variation of the practices was seen among hospitals within each country.

Antenatal corticosteroid administration to women with preterm birth at <34 weeks was infrequently used in most hospitals compared with other clinical practices in the antenatal period. The highest rate of antenatal corticosteroid use was 86% in a regional hospital in Thailand. In the Malaysian hospitals about half the women who gave birth at <34 weeks had been given antenatal corticosteroids. In the Indonesian hospitals this dropped to around 10% and in one tertiary hospital in The Philippines no administration of corticosteroids was recorded. Use of repeat courses of antenatal corticosteroids was less than 15% across all hospitals included in the audit.

Care practices during the intrapartum period (Table 3). Companionship in labour was assessed as to whether the woman had a family member present during childbirth. Rates for family support during labour varied widely, ranging from <1% at a Philippine hospital to 86% at a Malaysian hospital. Among the Malaysian hospitals the rates differed from 32% to 86%. In Thailand the rates of family support during labour were 31% at the university hospital, 44% at the provincial hospital and 83% at the regional hospital.

There were wide variations in the administration of an appropriate prophylactic oxytocic during third stage of labour both between countries and within countries. Rates for the administration of a uterotonic varied from <1% at one Philippine hospital to 98% at the Thai provincial hospital. Among the Thai hospitals rates of the practice were 4%, 76% and 98%. The variation was similar in The Philippines with one hospital giving oxytocics in two-thirds of cases and <1% in the other.

Controlled umbilical cord traction to deliver the placenta was routinely performed in the Indonesian, Malaysian and Philippine

Table 3. Percentage distribution of practices of beneficial forms of care

Care Practices	Indonesia			Malaysia			The Philippines			Thailand		
	Overall	Tertiary	District	Overall	Tertiary	District	Overall	Tertiary 1	Tertiary 2	Overall	Regional	University Provincial
<i>Antenatal period</i>												
MgSO ₄ for eclamptic fit	100	100	100	100	100	100	83	100	80	100	100	-
Antibiotic use for pPROM	91	88	100	62	83	100	92	99	67	73	91	63
MgSO ₄ for pre-eclampsia	100	100	100	24	44	100	100	91	100	64	57	67
Corticosteroids given to women who gave birth at <34 weeks	9	9	10	55	59	47	15	0	21	73	86	60
<i>Intrapartum period</i>												
Management of the third stage of labour												
Appropriate prophylactic oxytocic given during third stage	26	26	26	5	10	1	27	<1	64	58	4	98
Controlled cord traction to deliver the placenta	100	100	100	100	100	100	98	100	96	56	31	96
Family support during labour	41	38	45	61	86	32	10	<1	19	53	83	44
Appropriate antibiotic use for caesarean section	0	0	0	<1	<1	0	5	0	7	49	72	<1
<i>Postpartum period</i>												
Immunisation for Hepatitis B	2	0	3	99	99	99	2	<1	4	99	98	99

pPROM: preterm prelabour rupture of membranes, MgSO₄ : Magnesium Sulphate

Figures are percentages (rounded to the nearest whole number)

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hospitals. In Thailand, the rates were below 50% in the regional and tertiary hospitals but 96% in the provincial hospital.

Use of antibiotic prophylaxis for caesarean section in a single dose administered after clamping of the umbilical cord was mostly very low or non-existent across all the hospitals. About a quarter of women who gave birth by caesarean were given appropriate antibiotic prophylaxis (534 out of 2564), over 95% of these women were from two Thai hospitals.

Although antibiotics were often given in other hospitals, the timing of administration was preoperatively or postoperatively, and multiple doses were often prescribed.

Practices during postpartum period (Table 3). Immunising babies against the hepatitis B virus was the only postpartum neonatal care practice assessed in our project. This intervention was only routinely practiced in the Malaysian and Thai hospitals.

Forms of care likely to be ineffective or harmful (Table 4)

Episiotomy was the form of care likely to be harmful which was most frequently practiced across all the hospitals and in all four countries. The overall episiotomy rate for women giving birth vaginally was 65%. Episiotomies were liberally performed in all three hospitals in Thailand, and in only one Malaysian hospital did the rate drop below one-third. Pubic hair shaving, another ineffective and potentially harmful form of care, was commonly practiced in all countries with rates as high as 98% in one Thai hospital. In only one Philippine hospital was this observed as an occasional practice. Use of enemas during labour, an ineffective practice, was occasionally used in four hospitals across all countries and was highest in one Thai (61%) and one Malaysian (44%) hospital.

Discussion

This study describes the rates of use of selected practices of key aspects of perinatal care reported in the medical records of nine hospitals in Indonesia, Malaysia, The Philippines and Thailand. The findings show high rates of compliance for some evidence-based recommendations for perinatal care and wide divergence for others. Practices that were in line with recommendations across most hospitals for the beneficial forms of care were controlled cord traction, one of the components of the active management of the third stage of labour, and treating eclampsia with magnesium sulphate. The unnecessary practice of enema use was appropriately widely avoided. The highest level of divergence from best practice recommendations in most countries was not administering appropriate antibiotic prophylaxis for caesarean section. Liberal use of episiotomy for women having a vaginal birth is not recommended but was often inappropriately practiced across the hospitals in all four countries, demonstrating lack of adoption of the evidence-based recommendation of restrictive episiotomy. Other forms of perinatal care such as pubic hair shaving and the use of enemas during labour varied in rates of compliance across all countries and even between hospitals within the same country.

The principles of evidence-based practice are to encourage health professionals to use practices with proven benefit and eliminate the use of those shown to be ineffective or harmful. Effective implementation of beneficial practices in developing regions [9,10], such as South East Asia, should lead to a reduction in maternal and neonatal mortality and morbidities.

Our findings are consistent with three previous reports of perinatal practice from the Asian and Arab world [11–13]. The first was reported by the Choices and Challenges in Changing Childbirth Research Network [11]. The network documented routine obstetric practices for normal labour and birth in Egypt,

Table 4. Percentage distribution of practices of forms of care likely to be harmful

Care Practices	Indonesia			Malaysia			The Philippines			Thailand		
	Overall	Tertiary	District	Overall	Tertiary 1	Tertiary 2	Overall	Tertiary 1	Tertiary 2	Overall	Regional	University
Episiotomy for vaginal births	54	49	60	47	61	31	64	64	64	91	95	93
Public hair shaving	28	26	29	33	24	42	26	12	40	74	43	79
Enema use	17	17	18	22	2	44	1	<1	3	30	1	29
												61

Figures are percentages (rounded to the nearest whole number).
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Lebanon, Syria and the West Bank, and compared these with evidence-based recommendations. They showed the practices for normal labour were largely not in accordance with the World Health Organization evidence-based classification of practices for normal birth. The second report described facility-based practices for normal labour and birth [12]. Forty-four clinical practices observed in a busy Egyptian teaching hospital were categorised according to World Health Organization Technical Working Group on normal birth classification of normal birth practices. This study concluded that practices for normal labour were largely not consistent with the World Health Organization evidence-based classification of practices for normal births. The third report compared practices of selected childbirth care procedures against evidence-based information and explored user and provider views about each procedure in four hospitals in Shanghai, China [13]. They concluded that obstetric practices of the hospitals studied were not following best available evidence.

There is clear evidence of benefit to perinatal health outcomes with use of appropriate antibiotic prophylaxis for caesarean section, use of antenatal corticosteroids for women at risk of preterm birth and family support during labour. Our findings however, show that these clinical practices were rarely performed in most of the included hospitals, with high rates of variation across the countries. It is likely that there are a range of barriers to all these clinical practices in our study settings, but detailed exploration of these was outside the scope of this initial audit. Although we were not able to interview the care providers or directly observe the clinical practices at the time of this survey, these were planned for a later stage of this project.

Recommendation of use of appropriate antibiotic prophylaxis for caesarean section is defined as administration of a single dose of ampicillin or first generation cephalosporin after umbilical cord clamping of the baby [14]. We found that most non-concordant practices relating to antibiotic prophylaxis for caesarean section arose from giving multiple doses or administering antibiotics pre or post operatively. In some clinical settings multiple doses of antibiotics at pre-operative or post-operative times may be appropriate.

One advantage of our study was that the prospective, sequential collection of data provided accurate information of individual pregnant women and their babies, directly extracted from the medical records of individual pregnant women rather than derived from interviewing health care providers. In addition, the information was extracted prospectively and therefore the findings closely reflect the actual practices of perinatal health care in the nine hospitals of the four South East Asian countries. A limitation of such data collection is that there might be some interventions that were practiced but not well documented in medical records. However, this is likely to be minimal as most information in medical records of the hospitals involved in the study is standardised for the care practices considered.

In summary, few practices of perinatal health care in the nine hospitals within the four South East Asian countries were consistent with best available evidence from Cochrane reviews and the World Health Organization Reproductive Health Library recommendations. At the individual hospitals the audit results were used to evaluate the barriers to adoption of appropriate practices and elimination of inappropriate practices followed by strategies to increase the use of evidence-based practices in perinatal health care. The recording of clinical practices within this audit was a pre-requisite to identifying problems to be addressed.

Based on our findings, the SEA-ORCHID project team developed and implemented interventions that aimed to build

capacity for research conduct, synthesis and translation that would increase compliance with evidence-based clinical practice recommendations and so improve maternal and perinatal care.

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Research article

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Use of antenatal corticosteroids prior to preterm birth in four South East Asian countries within the SEA-ORCHID project

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Abstract

Background: There is strong evidence supporting the use of antenatal corticosteroids in women at risk of preterm birth to promote fetal lung maturation and reduce neonatal mortality and morbidity. This audit aimed to assess the use of antenatal corticosteroids prior to preterm birth in the nine hospitals in four South East Asian countries participating in the South East Asia Optimising Reproductive Health in Developing Countries (SEA-ORCHID) Project.

Method: We reviewed the medical records of 9550 women (9665 infants including 111 twins and two triplets) admitted to the labour wards of nine hospitals in four South East Asian countries during 2005. For women who gave birth before 34 weeks gestation we collected information on women's demographic and pregnancy background, the type, dose and use of corticosteroids, and key birth and infant outcomes.

Results: Administration of antenatal corticosteroids to women who gave birth before 34 weeks gestation varied widely between countries (9% to 73%) and also between hospitals within countries (0% to 86%). Antenatal corticosteroids were most commonly given when women were between 28 and 34 weeks gestation (80%). Overall 6% of women received repeat doses of corticosteroids. Dexamethasone was the only type of antenatal corticosteroid used.

Women receiving antenatal corticosteroids compared with those not given antenatal corticosteroids were less likely to have had a previous pregnancy and to be booked for birth at the hospital and almost three times as likely to have a current multiple pregnancy. Exposed women were less likely to be induced and almost twice as likely to have a caesarean section, a primary postpartum haemorrhage and postpartum pyrexia.

Infants exposed to antenatal corticosteroids compared with infants not exposed were less likely to die. Live born exposed infants were less likely to have Apgar scores of < 7 at five minutes and less likely to have any lung disease.

Conclusion: In this survey the use of antenatal corticosteroids prior to preterm birth varied between countries and hospitals. Evaluation of the enablers and barriers to the uptake of this effective antenatal intervention at individual hospitals is needed.

Background

Infants born preterm are at high risk of neonatal lung disease and associated complications [1]. Respiratory distress syndrome (RDS), a consequence of immature lung development, is the primary cause of early neonatal mortality [2] and contributes to significant immediate [1] and long-term morbidity in survivors [3]. Antenatal corticosteroid treatment for women at risk of very preterm birth before 34 weeks gestation is one of the most effective treatments for the prevention of RDS, reducing neonatal mortality and morbidity [4]. This is of importance for developing countries where resources are scarce and it is often difficult to provide expensive treatments such as neonatal care.

Although evidence of benefit for the use of antenatal corticosteroids has been available for many years [5,6], widespread adoption of this treatment into routine clinical practice was significantly delayed and implementation of their use remained suboptimal in developed countries for many years [7]. There is limited information as to how well this practice has been implemented in developing countries.

Objectives of this review

The aim of this audit was therefore to assess the use of antenatal corticosteroids for women who gave birth at less than 34 weeks gestation in the nine hospitals across four South East Asian countries within the South East Asia Optimising Reproductive Health in Developing Countries (SEA-ORCHID) Project [8]. Information was collated on which women received corticosteroids, their sociodemographics and obstetric history, the type, amount and reason for use of corticosteroids, the birth details and infant health outcomes.

Methods

Setting

Nine hospitals participating in the SEA-ORCHID project in four South East Asian countries namely Indonesia, Malaysia, the Philippines and Thailand were audited [9]. Seven of the nine hospitals were tertiary (university and regional) referral institutions with regional referrals of women with a high risk pregnancy and two hospitals were provincial or district institutions. Delivery care models included obstetric specialists or a multidisciplinary approach with midwives (including nurses with midwifery qualifications). In all hospitals obstetric specialists and caesarean section facilities were available and doctors and/or midwives (including nurses with midwifery qualifications) conducted normal vaginal births.

The SEA-ORCHID project settings and methods have been described elsewhere [8]. The study was approved as an audit by the local ethics committee of each hospital

and the administering institution in Australia. Individual patient consent was not therefore sought.

Procedure

Previously, as part of the SEA-ORCHID baseline data collection we completed a prospective audit of the medical records of 9550 women (9665 infants including 111 twins and two triplets) admitted to the labour wards at the nine participating SEA-ORCHID hospitals during 2005. At five of the participating hospitals medical records were audited on a consecutive basis until a sample of 1000 was reached. To reduce the risk of bias the four largest participating hospitals randomly sampled medical records using various ratios to ensure a sample of 1000 was reached over the three month data collection period.

For this current audit, staff at each hospital were trained to use pre-established data extraction forms to prospectively audit the medical records of the 290 women who gave birth at < 34 weeks regardless of whether they were given antenatal corticosteroids or not (Table 1). Data from each country was sent to Khon Kaen University by post where it was manually entered into a Microsoft Access 2003 database. The database minimised transcription errors by performing validation checks to detect discrepancies and missing data.

Demographic information collected about these women included maternal age, any previous birth ≥ 22 weeks, gestational age at time of last corticosteroid injection, if given, whether the pregnancy was singleton or twins, whether they received public or private care, whether they were booked for birth at the hospital and the main reason they were considered at risk of preterm birth (Table 2).

Health outcomes for all infants exposed to antenatal corticosteroids as well as those who were not were collected including gestational age at birth, birth weight, stillbirth, death prior to discharge, live born babies discharged alive, presence of respiratory distress syndrome, severity of any lung disease, use of oxygen therapy, use and duration of mechanical ventilation (defined as intermittent positive pressure ventilation and/or continuous airways pressure), Apgar scores and length of hospital stay (Table 3).

Maternal health outcomes of all women were collected including use of induction of labour, mode of birth, primary or major postpartum haemorrhage and postpartum pyrexia (Table 4).

Data Analysis

Descriptive statistics assessed the use of antenatal corticosteroids across countries and between hospitals within countries. Difference of means with 95% confidence interval (CI) was used to compare factors measured in

Table 1: Percentage distribution of women who gave birth at < 34 weeks GA and corticosteroid use

Countries	Hospitals	Number of women who gave birth at < 34 weeks n (%)	Antenatal corticosteroids given to women who gave birth at < 34 weeks n (%)
Indonesia	Overall	90 (4)	8 (9)
	Tertiary	69 (7)	6 (9)
	District	21 (2)	2 (10)
Malaysia	Overall	51 (2)	28 (55)
	Tertiary 1	32 (3)	19 (59)
	Tertiary 2	19 (2)	9 (47)
The Philippines	Overall	48 (2)	7 (15)
	Tertiary 1	15 (1)	0 (0)
	Tertiary 2	33 (3)	7 (21)
Thailand	Overall	101 (3)	74 (73)
	Regional	51 (5)	44 (86)
	University	25 (3)	15 (60)
	Provincial	25 (3)	15 (60)

Figures are numbers with percentages rounded to the nearest whole number in brackets.

continuous data, such as maternal age and birth weight, between the two groups. When the data were skewed, difference of medians with 95% CI was used. Independent t-test or Mann-Whitney U test, where appropriate, was used for significant comparison of the two groups and results were shown as p-values. Relative risk (95% CI) and Chi-square tests were used for comparing the factors measured

in categorical data, such as parity and multiple pregnancy between the two groups. The analysis was done using STATA software version 8.0 [10].

Ethics

The SEA-ORCHID project was approved by the local ethics committees of each hospital and by the ethics commit-

Table 2: Characteristics of women receiving/not receiving antenatal corticosteroids with birth 24 to < 34 weeks gestational age

	Antenatal corticosteroids		Comparative statistic [#]	95% CI	p-value
	Received n = 104	Not received n = 148			
Maternal Age* (years)	27.6 (6.8)	28.5 (6.9)	-0.85	-2.59; 0.88	0.34
Parity ‡					
Previous pregnancies ≥ 22 weeks	47 (45)	86 (58)	0.77	0.60; 0.99	0.04
Gestational age at last injection					
< 24 – 27 weeks	20 (19)	-	N/A	N/A	N/A
28 – 31 weeks	42 (40)	-			
32 – < 34 weeks	42 (40)	-			
Multiple pregnancy					
Twins	10 (10)	5 (3)	2.84	1.0; 8.1	0.04
Patient status ‡					
Public	98 (94)	144 (98)	0.96	0.91; 1.01	0.12
Booked for birth at hospital ‡	81 (79)	136 (92)	0.86	0.77; 0.96	0.01
Main reasons for risk of preterm birth					0.01
Preterm labour	42 (40)	36 (24)	-	-	
PPROM	26 (25)	19 (13)	-	-	
Hypertension	18 (17)	18 (12)	-	-	
APH	6 (6)	9 (6)	-	-	
Maternal conditions	4 (4)	6 (4)	-	-	
Multiple pregnancy	2 (2)	2 (1)	-	-	
Fetal concern	1 (1)	8 (5)	-	-	
Other/not recorded	5 (5)	50 (34)	-	-	

Figures are numbers with percentages rounded to the nearest whole number in brackets and with relative risk and 95% confidence intervals as the comparative statistic[#], or *Mean and standard deviation with mean difference between groups and 95% confidence intervals as the comparative statistic[#]. ‡Outcomes not available for a few women

Table 3: Health outcomes for infants exposed to antenatal corticosteroids versus those not exposed

	Antenatal corticosteroids		Comparative statistic [#]	95% CI	p-value
	Exposed	Not exposed			
All babies	n = 114	n = 152			
Gestational age at birth* [‡] (weeks.days)	30.4 (2.6)	29.9 (2.7)	0.47	-0.19; 1.13	0.16
Birth weight* [‡] (kg)	1.62 (0.65)	1.48 (0.63)	0.14	-0.02; 0.29	0.08
Stillbirth	2 (2)	42 (28)	0.06	0.02; 0.25	0.01
All deaths (stillbirths/deaths prior to discharge)	18 (16)	49 (32)	0.49	0.30; 0.79	0.01
Mode of birth					0.01
normal vaginal	59 (52)	99 (65)	1	--	--
vaginal breech	4 (4)	19 (13)	0.39	0.14; 1.11	0.06
operative vaginal birth	2 (2)	2 (1)	1.65	0.24; 11.45	0.63
caesarean section	49 (43)	32 (21)	1.85	1.28; 2.67	0.01
Live born babies	n = 112	n = 111			
Live born babies discharged alive	96 (86)	103 (93)	0.92	0.84; 1.0	0.05
Respiratory distress syndrome ^{‡‡}	59 (60)	54 (57)	1.06	0.83; 1.34	0.64
Severity of lung disease [§]					0.01
none	22 (30)	4 (11)	1	--	--
mild	7 (9)	15 (42)	--	--	--
moderate	27 (37)	6 (17)	--	--	--
severe	18 (24)	11 (30)	--	--	--
Use of oxygen therapy [¶]	50 (50)	55 (57)	0.86	0.66; 1.12	0.27
Use of mechanical ventilation ^{¶¶}	53 (54)	25 (39)	1.38	0.97; 1.98	0.06
Apgar Score < 7 at 1 min [†]	42 (38)	57 (52)	0.73	0.54; 0.98	0.04
Apgar Score < 7 at 5 min [†]	15 (14)	34 (31)	0.44	0.25; 0.75	0.01

Figures are numbers with percentages rounded to the nearest whole number in brackets and with relative risk and 95% confidence intervals as the comparative statistic[#], or *mean and standard deviation with mean difference between groups and 95% confidence intervals as the comparative statistic[#]. [§]Severity of lung disease is defined as none (no oxygen required), mild (Oxygen < 40% FiO₂), moderate (FiO₂ 40–79%), severe (FiO₂ 80% or more). [‡]Values are based on 114 in the Exposed Group and 151 in the Not Exposed Group. ^{‡‡}Values are based on 98 in the Exposed Group and 95 in the Not Exposed Group. [¶]Values are based on 101 in the Exposed group and 96 in the Not Exposed Group. ^{¶¶}P Values are based on 98 in the Exposed Group and 64 in the Not Exposed Group. [†]Values are based on 111 in the Exposed Group and 110 in the Not Exposed Group.

tee of the University of Sydney, the administering institution in Australia.

Results

Corticosteroid administration in South East Asian countries (Table 1)

Antenatal corticosteroids were not frequently administered to women who gave birth at less than 34 weeks gestation at any of the hospitals audited across the four South East Asian countries. Of the 290 women who gave birth at less than 34 weeks gestation presenting to the audited hospitals, 117 (40%) received antenatal corticosteroids.

Thai and Malaysian hospitals showed the highest usage of antenatal corticosteroids for women who gave birth before 34 weeks gestation (73% and 55% respectively). Less than 10% of women who gave birth preterm at Indonesian hospitals were reported to be given antenatal corticosteroids. Hospitals in The Philippines recorded a low rate of antenatal corticosteroid use with one hospital not administering corticosteroids to any women who gave birth preterm.

Table 4: Maternal outcomes for women receiving/not receiving antenatal corticosteroids with birth 24 to < 34 weeks gestational age

	Antenatal corticosteroids		Relative Risk	95% CI	p-value
	Received n = 104	Not received n = 148			
Induction of labour [‡]	3 (3)	11 (23)	0.14	0.04; 0.47	0.01
Primary postpartum haemorrhage (≥ 500 ml) [‡]	27 (26)	22 (15)	1.68	1.02; 2.79	0.04
Major haemorrhage (≥ 1000 ml) [‡]	8 (8)	7 (5)	1.57	0.58; 4.19	0.42
Postpartum pyrexia ≥ 38°C [‡]	9 (9)	2 (1)	6.53	1.44; 29.5	0.01

Figures are numbers with percentages rounded to the nearest whole number in brackets and with relative risk and 95% confidence intervals as the comparative statistic. [‡]Outcomes not available for a few women.

Dexamethasone was the only antenatal corticosteroid used across the nine hospitals. Repeat courses of antenatal corticosteroids were given to 6% of women.

Maternal demographics (Table 2)

Overall, women who gave birth at less than 34 weeks gestational age who received antenatal corticosteroids were similar in age to women who did not receive antenatal corticosteroids (mean maternal age 27.6 years (Standard Deviation (SD) 6.8) and 28.5 years (SD 6.9) respectively). Nearly all women in this audit attended a public hospital throughout their pregnancy. Compared with women who did not receive antenatal corticosteroids, women who did were less likely to have had a previous pregnancy ≥ 22 weeks (RR 0.77, [95%CI 0.60, 0.99], $p = 0.04$), almost three times as likely to have a multiple pregnancy (RR 2.84, [95%CI 1.0, 8.1], $p = 0.04$) and less likely to be booked for birth at the hospital (RR 0.86, [95%CI 0.77, 0.96], $p = 0.01$). For women receiving antenatal corticosteroids, most had their last injection after 28 weeks gestation. Similar numbers of women received their last injection between 28 to 31 weeks and between 32 to < 34 weeks gestation (40% and 40%).

There were significant differences in the distributions of the main reason women were considered at risk of preterm birth between the mothers who were administered corticosteroids and those who did not receive them ($p = 0.01$) (Table 2). More women who received antenatal corticosteroids were in preterm labour, or had preterm prelabour rupture of the membranes or hypertension.

Although health outcomes for the mother and their infants are compared below by whether exposed or not to antenatal corticosteroids, it needs to be remembered these are not randomised groups. Groups may well differ by other factors influencing health outcomes besides the exposure or not to corticosteroids.

Infant health outcomes (Table 3)

Infants exposed to antenatal corticosteroids were born at a similar gestational age and had similar birth weights to infants who were not exposed. The majority of infants in both groups were born between 28 to < 34 weeks (82% and 80% respectively). Infants exposed to antenatal corticosteroids were less likely to be stillborn (RR 0.06, [95%CI 0.02, 0.25], $p = 0.01$) and were less likely to die prior to hospital discharge (stillbirth and death prior to discharge combined, RR 0.49, [95%CI 0.30, 0.79], $p = 0.01$) compared with infants who were not exposed. Live born infants who were not exposed were more likely to be discharged alive than infants who were exposed to antenatal corticosteroids (RR 0.92, [95%CI 0.84, 1.0], $p = 0.05$).

The distribution of severity of any lung disease was significantly different in infants exposed to antenatal corticosteroids with fewer infants having respiratory problems compared with infants who were not exposed ($p = 0.01$). Low Apgar scores (< 7) at 1 minute and 5 minutes were less likely for infants exposed to antenatal corticosteroids compared with infants who were not exposed (RR 0.73, [95%CI 0.54, 0.98], $p = 0.04$ and RR 0.44, [95%CI 0.25, 0.75], $p = 0.01$ respectively).

The risk of respiratory distress syndrome, use of mechanical ventilation and use of oxygen therapy were not statistically different between the two groups of infants.

Maternal health outcomes (Table 4)

Significantly fewer women who received antenatal corticosteroids were induced (RR 0.14, [95%CI 0.04, 0.47], $p = 0.01$) however they were almost twice as likely to have a caesarean section (RR 1.85, [95%CI 1.28, 2.67], $p = 0.01$) compared with women who did not receive antenatal corticosteroids. A primary postpartum haemorrhage (≥ 500 ml) was more likely for women who received antenatal corticosteroids (RR 1.68, [95%CI 1.02, 2.79], $p = 0.04$) and they were over six times more likely to develop a postpartum pyrexia ($\geq 38^\circ\text{C}$) compared with women who did not receive them (RR 6.53, [95%CI 1.44, 29.5], $p = 0.01$).

Discussion

An audit by the SEA-ORCHID group across four South East Asian countries found the use of antenatal corticosteroids to be one of the least performed beneficial interventions in the prenatal period at collaborating hospitals within those countries [9]. We therefore conducted this in depth review of antenatal corticosteroid use prior to preterm birth in women presenting to the nine hospitals in four South East Asian countries to compare sociodemographic factors, obstetric history and birth and infant outcomes between women exposed and non-exposed.

This review reported varying uptake of these guidelines into practice both between the nine hospitals in the four South East Asian countries that were audited and between the countries themselves. Within the countries, there was no obvious relationship between the type of hospital and the implementation of the use of corticosteroids, as use varied between hospitals within some countries and was similar between hospitals in other countries. These findings highlight the need to examine the barriers and enablers to adoption of the use of antenatal corticosteroids among maternal and infant health practitioners at the individual hospitals. Furthermore, it illustrates potential benefit in each hospital developing its own locally relevant clinical practice guideline for antenatal corticosteroid administration so as to encourage standardised best practice.

The results of our review show that women from the nine collaborating hospitals who received antenatal corticosteroids were more likely to be experiencing their first pregnancy and have a multiple pregnancy but were less likely to be booked at the hospital for birth. There remains doubt about the use of antenatal corticosteroids in multiple pregnancies. One study has reported similar risks of death or major morbidity between singleton and multiple infants [11] while other studies suggest that antenatal corticosteroid therapy does not significantly reduce the incidence of respiratory distress syndrome in multiple gestations [12-15]. Further analysis of health outcomes of infants from multiple pregnancies need to be analysed to provide evidence either for or against this practice [4].

Our review showed that in the nine hospitals in the four South East Asian countries audited, over 80% of corticosteroids administered were given when women were over 28 weeks gestation. Gestational age at which antenatal corticosteroids should be given has long been a topic of debate. An earlier systematic review showed limited evidence of benefit if given at less than 28 weeks [16] although the updated systematic review shows respiratory distress syndrome is reduced when corticosteroids are given in multiple doses with the first injection between 26 to 29.9 weeks [4].

The type of antenatal corticosteroid used between countries and between hospitals within countries did not differ, with dexamethasone the only corticosteroid used. It is recognised that the frequency of respiratory distress syndrome is decreased by both betamethasone and dexamethasone [4], although there is still uncertainty concerning which corticosteroid provides better health outcomes [17].

The reason as to only dexamethasone being used in the South East Asian countries audited is most likely due to financial reasons, given that dexamethasone is the less expensive of the two corticosteroids. As a result of this, dexamethasone is often simply the only drug available in these developing countries.

Limited use of repeat steroids was reported for all four South East Asian countries. Evidence for the use of a single course of antenatal corticosteroids for women at risk of preterm birth has been acknowledged and accepted and it has become recommended standard care [7,18,19]. At the time of this audit, evidence regarding the effects of repeat courses of antenatal corticosteroids was still unclear [20].

The published systematic reviews on antenatal corticosteroids papers [4] report positive health outcomes for mothers and infants. The few negative health outcomes seen in

our audit are likely to reflect selection bias due to the use of selective, non randomised groups.

Based on abundant evidence suggesting that antenatal corticosteroids positively influence infant survival for preterm birth, and the audit result of varying uptake of this intervention in the participating hospitals, it is obvious that barriers to uptake of practice, in particular access to evidence-based practice guidelines and recommendations need to be examined at the individual institutions. As part of the SEA-ORCHID project we plan to conduct a survey of evidence-based practice knowledge and clinical change among maternal and infant health practitioners in South-East Asia to explore this issue.

A similar intervention undertaken in Thailand increased the rate of use of antenatal corticosteroids for women who gave birth preterm (< 34 weeks gestation) from a baseline rate of 41% to 73% after evidence became available and was disseminated [21]. Prior to this intervention an increase from 33% to 58% for the rate of antenatal corticosteroid administration in the US was achieved after distribution of information. A further increase to 68% was achieved after further knowledge of evidence distribution [22].

Conclusion

This audit across four South East Asian countries indicates that rates of use of antenatal corticosteroids are varied in the hospitals participating in the SEA-ORCHID project. Antenatal corticosteroids given to women prior to preterm birth had significant health benefits for their babies. The findings of this review highlight an important gap in best practice recommendations that could be improved with relatively low cost and with great benefit to neonatal outcomes in resource poor countries. Barriers to uptake and implementation of evidence-based practice guidelines need to be evaluated and addressed and form part of the ongoing SEA-ORCHID project [8].

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

PL, ML, SM and CC contributed to the design of the study. PP cleaned and analysed the data and all authors contributed to the interpretation of data. ME prepared the first draft of the paper. All authors commented on each draft of the paper.

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Study protocol

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Active management of the third stage of labour without controlled cord traction: a randomized non-inferiority controlled trial

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Abstract

Background: The third stage of labour refers to the period between birth of the baby and complete expulsion of the placenta. Some degree of blood loss occurs after the birth of the baby due to separation of the placenta. This period is a risky period because uterus may not contract well after birth and heavy blood loss can endanger the life of the mother. Active management of the third stage of labour (AMTSL) reduces the occurrence of severe postpartum haemorrhage by approximately 60–70%. Active management consists of several interventions packaged together and the relative contribution of each of the components is unknown. Controlled cord traction is one of those components that require training in manual skill for it to be performed appropriately. If it is possible to dispense with controlled cord traction without losing efficacy it would have major implications for effective management of the third stage of labour at peripheral levels of health care.

Objective: The primary objective is to determine whether the simplified package of oxytocin 10 IU IM/IV is not less effective than the full AMTSL package.

Methods: A hospital-based, multicentre, individually randomized controlled trial is proposed. The hypothesis tested will be a non-inferiority hypothesis. The aim will be to determine whether the

simplified package without CCT, with the advantage of not requiring training to acquire the manual skill to perform this task, is not less effective than the full AMTSL package with regard to reducing blood loss in the third stage of labour.

The simplified package will include uterotonic (oxytocin 10 IU IM) injection after delivery of the baby and cord clamping and cutting at approximately 3 minutes after birth. The full package will include the uterotonic injection (oxytocin 10 IU IM), controlled cord traction following observation of uterine contraction and cord clamping and cutting at approximately 3 minutes after birth. The primary outcome measure is blood loss of 1000 ml or more at one hour and up to two hours for women who continue to bleed after one hour. The secondary outcomes are blood transfusion, the use of additional uterotonics and measure of severe morbidity and maternal death.

We aim to recruit 25,000 women delivering vaginally in health facilities in eight countries within a 12 month recruitment period.

Management: Overall trial management will be from HRP/RHR in Geneva. There will be eight centres located in Argentina, Egypt, India, Kenya, Philippines, South Africa, Thailand and Uganda. There will be an online data entry system managed from HRP/RHR. The trial protocol was developed following a technical consultation with international organizations and leading researchers in the field.

Expected outcomes: The main objective of this trial is to investigate whether a simplified package of third stage management can be recommended without increasing the risk of PPH. By avoiding the need for a manual procedure that requires training, the third stage management can be implemented in a more widespread and cost-effective way around the world even at the most peripheral levels of the health care system. This trial forms part of the programme of work to reduce maternal deaths due to postpartum haemorrhage within the RHR department in collaboration with other research groups and organizations active in the field.

Trial Registration: ACTRN12608000434392

Background

The third stage of labour refers to the period between birth of the baby and complete expulsion of the placenta. Some degree of blood loss occurs after the birth of the baby due to separation of the placenta. This period is a risky period because uterus may not contract well after birth and heavy blood loss can endanger the life of the mother.

The third stage of labour is managed differently around the world. Over the years two management packages, known as 'active management' and 'expectant management' emerged. The primary aim of active management is to reduce postpartum blood loss as a preventive intervention. In active management (AMTSL) a number of interventions are applied in combination while the expectant management represents a more hands-off style with those interventions used in AMTSL withheld. AMTSL has been defined in various ways and current international definition comprises three components: administration of an uterotonic soon after delivery of the baby; controlled cord traction; and uterine massage after delivery of the placenta [1]. Active management of the third stage of labour (AMTSL) reduces the occurrence of severe postpartum haemorrhage by approximately 60–70% [2].

In previous active versus expectant trials the cord was clamped as soon as possible usually within one minute. However, trials of cord clamping timing have shown beneficial effects on newborn haematological indices leading to the recommendation to clamp the cord at around 3 minutes although the effects on the mother are unknown [3].

The WHO PPH Prevention Guidelines published in 2007 recommended AMTSL defined as the use of oxytocin 10 IU IM/IV after birth, cord clamping at around 3 minutes when the uterus contracts and controlled cord traction. There were no recommendations related to the use of uterine massage in this guideline.

Unfortunately, the relative contribution of the components of AMTSL to the overall reduction in blood loss is not clearly known. Understanding the contribution of the components of AMTSL to the overall effect in reducing the incidence of haemorrhage could have major programmatic significance since some components require training while others require an efficient drug procurement and utilization system [4]. At the same time the probability of interaction between AMTSL components should be kept in mind.

These considerations led to a technical consultation of scientists working in the field of postpartum haemorrhage research in December 2007 to discuss work on a research project to evaluate the effects of different components of AMTSL. Such research is important and timely because some components such as the uterotonic and controlled cord traction may not be feasible in all settings and it is worthwhile evaluating a more simple package with fewer components.

Systematic reviews of effects of AMTSL components

Uterotonic

The uterotonic component of AMTSL seems to be important for the reduction in blood loss after delivery [5]. Two trials compared oxytocin to nothing without other active management components practiced [6,7] and one trial compared oxytocin to nothing with other active management components practiced in both groups [8]. Oxytocin used at 5–10 IU seemed to reduce the risk of severe postpartum haemorrhage although the other components were not well described.

Controlled cord traction

Cord traction was introduced into obstetric practice by Brandt (1933) and Andrews (1940) by the so-called Brandt-Andrews maneuver. The aim is to facilitate the delivery of a placenta that is already separated. In 1962 the term *controlled cord traction* (CCT) was introduced which aims to facilitate the separation of the placenta once the uterus contracts [9]. In performing CCT placental separation is not waited and once the uterus contracts the CCT is initiated. The third stage is usually completed in less than 10 minutes when CCT is used.

There is concern by clinicians, based on teachings from their pre-service education that traction on the cord prior to placental separation may lead to maternal complications such as separation of the cord from the placenta and uterine inversion. There is not a large body of direct evidence for or against effects of controlled cord traction in isolation [10].

CCT requires training to acquire this manual skill. Evaluation of CCT component is important because if it does not add any beneficial effects it can be dropped from the AMTSL package with important programmatic implications.

Uterine massage

Uterine massage is used following delivery in various forms. Between delivery of the baby and the placenta a birth attendant will often put his/her hand over the uterus to ensure that there is no undiagnosed twin, to assess if the uterus is contracting and may rub the uterus to stimulate contraction. The Cochrane review on active

versus passive management does not refer to the use of uterine massage as part of AMTSL whereas the FIGO/ICM statement on AMTSL does include uterine massage as part of AMTSL. Evidence that massage contributes to a reduction in blood loss would provide evidence to support the use of this intervention with simple instructions.

The National Institute for Health and Clinical Excellence of the United Kingdom published comprehensive guidelines on intrapartum management on 26 September 2007 <http://www.nice.org.uk/nicemedia/pdf/IPCNICEGuidance.pdf> and has made no reference to uterine massage.

A small pilot trial (n = 200) conducted in Assiut, Egypt, used 'sustained uterine massage' started after delivery applied every 10 minutes and continued for 60 minutes. The findings are promising, since women receiving massage had less blood loss > 500 ml and received less additional uterotonics than women not receiving uterine massage [11]. In the two surveys conducted by Prevention of Postpartum Hemorrhage Initiative (POPHI) massage before placental delivery was practiced in about one third of all deliveries. In the same surveys massage after placental delivery was used in 80–90% of women although it was not possible to observe how long after delivery the massage was continued [12].

Williams Obstetrics states "massage is not employed but the fundus is frequently palpated to make certain that the organ does not become atonic and filled with blood from placental separation". In the United States and some other countries, palpating the uterus and massaging if "soft" for the first few hours after childbirth is considered standard of care [13]. In many countries however, no well-defined massage protocol exists. A systematic review to evaluate the effects of sustained uterine massage from the time of birth of the baby currently contains very little evidence to guide practice [14].

Other interventions

One intervention that has recently been included in AMTSL package is delayed cord clamping. There is evidence that delayed cord clamping increases newborn haematological indices in the short term and also has beneficial effects of reduced intraventricular haemorrhage when applied to preterm infants. However, there is almost no evidence on maternal effects especially whether it increases the blood loss.

Other third stage interventions include squeezing the uterus from the fundus to expel the placenta (Credé maneuver) [15], placental cord drainage, umbilical vein injection and variations in timing, dose, and route of above discussed components.

Rationale for selecting the experimental intervention

An important aspect of AMTSL components is that one cannot assume that each component has no interaction with others. Such interactions could occur for single, double or triple components. The implication is that even if an intervention may not be (as) effective when individually applied it may have effect together with another component. For example, oxytocin and massage could act synergistically.

The relative importance of all of these uncertainties and the feasibility of evaluating the effects of one or more of the components were discussed in detail at the technical consultation referred above in December 2007. The evaluation of two components namely CCT and uterine massage after placental delivery was given priority. The feasibility of evaluating both interventions in one trial was discussed in detail. Different epidemiological designs such as three-arm and 2×2 factorial design were considered. Evaluating more than one component in a single trial posed particular difficulties. Such difficulties originated from the nature of the intervention(s) (manual procedures being difficult to mask) and the low incidence of the primary outcome measure. The implications of these two factors were resorting to cluster or cross-over cluster designs with added complexity and large sample sizes. At the end of the consultative process evaluation of a package that does not include controlled cord traction was regarded as the highest priority research question among all discussed. The main reason for this conclusion is that currently, the global scale up of AMTSL is limited to those settings where skilled birth attendants are available largely because controlled cord traction (CCT) requires clinical skills training. Considerable training investments are needed to enable health providers to do CCT correctly and safely.

The presence of a skilled birth attendant is essential in every childbirth. Birth attendants are required for not only basic care during the first and second stage of labour but also in the third stage when haemorrhage risk is greatest and also for the immediate care of the newborn. We aim to identify the relative effect of one component that requires manual skill training. In the most peripheral points of the health system the availability of health personnel with skills to implement the full AMTSL package may be more difficult to ensure in some settings. Therefore, evaluation of whether a simplified package without CCT is non-inferior to the full AMTSL package has both clinical and public health importance. The simplified package is also less intrusive for the mother.

If it were possible to demonstrate the non-inferiority of a simplified form of AMTSL, dispensing with CCT, it would greatly reduce programme costs associated with training,

and enable the intervention to be used by lower level providers, especially in out-of-hospital settings.

We therefore put forward the hypothesis that a simplified package comprising oxytocin 10 IU IM/IV (with or without uterine massage) is as effective as the full AMTSL package.

Objective

The primary objective is to determine whether the simplified package of oxytocin 10 IU IM/IV, without CCT, is not less effective than the full AMTSL package with regard to reducing blood loss ≥ 1000 ml in the third stage of labour. The hypothesis will be that of non-inferiority within a margin of 0.45 to 0.50%. If this hypothesis is demonstrated, the simplified package without CCT could be adopted, with the advantage of not requiring training to acquire the manual skill to perform this task.

Study design

This will be a hospital-based, multicentre, individually randomized non-inferiority controlled trial.

Each woman will be randomized to receive either the full (AMTSL) package or the simplified package. The blinding of the intervention will not be possible because the comparison includes a manual procedure.

Interventions

In order to overcome the variations in the actual practice of AMTSL a working definition was discussed and agreed upon during the technical consultation.

Experimental arm: Simplified package

The simplified package will include;

• Uterotonic

Oxytocin 10 IU IM. Oxytocin will be administered as soon as possible after birth preferably within one minute. If a woman has an IV line oxytocin can be administered through the IV line by slow injection.

• Cord clamping

Cord will be clamped following observation of a uterine contraction either manually or visually. For practical purposes this is estimated to be around 1–3 minutes. It is recommended to clamp the cord close to the perineum.

• Placental delivery

Cord traction is omitted. Placenta should be delivered passively by aid of gravity and maternal effort. The caregiver should observe the placental separation and as the placenta delivers it should be held in two hands and gently turned so that the membranes do not tear off.

• Uterine massage

No uterine massage is recommended before placental delivery. After placental delivery the uterus will be rubbed and any clots expressed. For a period of two hours the uterus will be massaged gently until it contracts and this procedure will be repeated every 15 minutes. It is acknowledged that not all centres will be able to implement this component. Each centre will decide before the trial begins whether the uterine massage component will be implemented or not.

Standard intervention arm: Full AMTSL package

The full package will include:

• Uterotonic

Oxytocin 10 IU IM. Oxytocin will be administered as soon as possible after birth preferably within one minute. If a woman has an IV line oxytocin can be administered through the IV line by slow injection.

• Cord clamping

Cord will be clamped following observation of a uterine contraction either manually or visually. For practical purposes this is estimated to be around 1–3 minutes. It is recommended to clamp the cord close to the perineum.

• Placental delivery

Placenta will be delivered by controlled cord traction immediately after cord clamping and cutting. The cord will be gently pulled while applying counter traction to the uterus with the other hand. As the placenta delivers it should be held in two hands and gently turned so that the membranes do not tear off.

• Uterine massage

No uterine massage is recommended before placental delivery. After placental delivery the uterus will be rubbed and any clots expressed. For a period of two hours the uterus will be massaged gently until it contracts and this procedure will be repeated every 15 minutes. It is acknowledged that not all centres will be able to implement this component. Each centre will decide before the trial begins whether the uterine massage component will be implemented or not.

The two intervention packages will differ only in placental delivery technique. If the umbilical cord has been clamped early because of newborn indication cord traction should be applied only after the uterus has contracted as above.

Outcome measures

The primary outcome measure is blood loss of 1000 ml or more at one hour and up to two hours for women who continue to bleed after one hour. Blood collection will be made using the calibrated drape BRASSS-V® and measured

from delivery to one hour following delivery or up to two hours if bleeding continues [16].

Secondary outcomes are;

- blood transfusion,
- the use of additional uterotonics to treat PPH
- blood loss 500 ml or more
- postpartum maternal haemoglobin (in centres where feasible)
- maternal death
- manual removal of placenta,
- additional surgical procedures (e.g. hysterectomy, ligation of vessels)
- composite outcome of maternal death or severe morbidity (admission to intensive care unit, hysterectomy, blood loss of two liters or more, uterine inversion, near miss event as defined in the manual of operations)
- initiation of breastfeeding
- side effects such as nausea and abdominal pain

Once the cord is clamped and cut the drape will be placed under the woman's buttocks and blood loss measurement will begin. The blood loss measurement will continue for one hour regardless of whether the woman is kept in the delivery room or moved elsewhere. If the bleeding continues beyond one hour the blood loss measurement will continue until two hours postpartum.

Side effects will be recorded by the researcher. Any side effect requiring treatment will be regarded as an adverse event and a separate form will be filled.

Serious adverse events will be recorded in special forms and will be returned by the local investigators to the trial coordination unit within 24 hours.

Study population

All women expecting to deliver vaginally at the participating hospitals will be potentially eligible. Women will be approached primarily during antenatal care and early labour for consent for participation except under the following circumstances;

1. Advanced first stage of labour (> 6 cm cervical dilatation)

2. Women who are too distressed to give consent regardless of cervical dilatation or phase of labour. Such evaluation will be made by the clinician in charge of the care of the woman.

3. Minors without a guardian

4. Planned caesarean section

5. If the birth is considered an abortion according to local limits

6. Women with twins or higher order multiple gestations

7. Women who are not capable of giving consent due to other health problems such as obstetric emergencies (e.g. eclampsia) or mental disorder.

Women receive AMTSL regardless of whether they are at high or low-risk for haemorrhage. Therefore all women will be eligible for participation according to the exceptions mentioned above.

Methods

Generation of allocation sequence

The random allocation sequence will be generated centrally at WHO Headquarters using computer generated random numbers. Randomization will be to two groups and stratified by country. Blocking with randomly varying groups of 6–8 will be used to restrict randomization within the strata.

Random allocation technique and allocation concealment

Allocation of the random generated sequence will be by consecutively numbered envelopes. Allocation concealment will be achieved by using sealed opaque envelopes. Allocation will take place during second stage when vaginal delivery is imminent. Once the envelope is opened the name of the woman will be entered on the log file with the envelope number and that woman is enrolled in the trial.

Rationale for the non-inferiority hypothesis and for sample size estimation

The objective of this trial is to show 'non-inferiority' of the simplified package' compared to the full AMTSL package. As such, while superiority would be an added bonus it is not expected and is probably not plausible since the experimental intervention has fewer interventions.

In the conventional superiority trial, the aim is to determine whether one intervention is superior to another, for example, whether uterotonic is superior to nothing. By contrast, in a non-inferiority trial, the aim is to determine whether an alternative intervention with certain advantages

is similar to a gold standard. The full AMTSL package represents the gold standard management strategy for reducing blood loss in the third stage of labour. In order to evaluate the effectiveness of a simplified package with fewer components that package has to be compared to the full package to see whether it is "non-inferior" to the gold standard [17].

Because proof of exact equality is impossible, a pre-stated margin of non-inferiority (Δ) for the difference in effectiveness has to be defined. The choice of the non-inferiority margin can be made using clinical assessment, which is to a certain extent arbitrary, and needs consensus among different stakeholders. A technique which has been proposed [17] to establish the non-inferiority margin is to look at the effect of the gold standard, in this case the full AMTSL, compared with placebo in historical (past) trials, in this case the expectant management. A reasonable criterion is to preserve 80% of the benefit of the full AMTSL package (considered as 100%) over expectant management (considered as 0%). Preserving a higher percentage (say 90%) will push the sample size calculations very high while a smaller percentage (say 50%) may not be considered acceptable.

Estimates of blood loss ≥ 1000 ml (severe PPH – sPPH) with active and passive management were taken from the literature. In addition, unpublished data from several ongoing WHO studies where postpartum blood loss is measured were obtained. Based on those data, a 1.5% risk of blood loss of 1000 ml with full active management was considered realistic and appropriate.

The expectant management sPPH rate was more difficult to estimate because the data was only available from earlier published trials and blood loss estimation methods and the actual expectant management method differed between trials. Values between 3.0 to 4.0% are considered realistic and used for sample size estimations.

Table 1 includes different scenarios for the calculation of sample size, obtained by varying the sPPH rate with expectant management (3.0 to 4.0%) and varying the % retained effect (70% to 80%), assuming a fixed 1.5% sPPH rate for the full AMTSL package. These different scenarios result in different choices of the margin of non-inferiority Δ . The total sample size required for a non-inferiority test at the 2.5% level using a two-sided 95% confidence interval and a power of 80% is shown, as well as the power obtained for fixed sample sizes of 20,000 and 25,000.

A trial of 22,908 women will have 80% power to show non-inferiority of the simplified package within 0.45% of the full AMTSL package sPPH rate (i.e. less than 1.95%

Table 1: Sample size scenarios

Blood loss $\geq$ 1000 ml with full amtsl	Blood loss $\geq$ 1000 ml with Expectant	Estimated impact of Full AMTSL	Proportion (of full AMTSL effect) retained by the simplified package	Δ (Difference to exclude to claim equivalence)	Total N for 80% Power	Power with total N = 20,000	Power with total N = 25,000
1.5	3.0	1.5	0.7	0.45	22,908	75%	83%
1.5	3.5	2.0	0.75	0.50	18,555	83%	90%
1.5	4.0	2.5	0.8	0.50	18,555	83%	90%

sPPH rate), with a level of significance of 2.5% (Table 1, row 1). The estimates from the centres that have expressed interest in participating in the trial indicate that approximately 20,000–25,000 women can be recruited in a 12 months recruitment period. These centres have collaborated with WHO before and have experience in third stage trials.

Type of data and data collection procedure

The trial will be conducted in the labour ward of maternity facilities. All women with anticipated vaginal delivery will be eligible. During the trial period information on the total number of births in the facility will be collected to monitor the recruitment efficiency. Ideally, the participating centres should enroll women 24 hours a day. However, such recruitment may not be possible at all centres.

The main data collection will be during the immediate postpartum period but women will be followed up until discharge from the hospital to record any additional interventions and complications that may occur. Once the bleeding stops and the woman is ready for transfer to the postnatal ward the researcher will fill the data collection form. After discharge the data collection forms will be completed and the form data will be entered on to the online system. The online data entry will be either at the hospital or country level depending on local capacity.

Analysis plan

The main analysis will be on an intention-to-treat principle with comparisons made between the 'simplified' and 'full' AMTSL packages for primary and secondary outcomes. An alternative to the ITT analysis (non-ITT analysis, sometimes called 'per-protocol'), that excludes patients not on their intended treatment and/or those who are not protocol-compliant in any other way could bias the trial in either direction, depending on which patients are thus excluded. In non-inferiority and equivalence trials, performing non-ITT analysis in addition to ITT analysis is desirable as a protection from the increase in type I error risk.

We expect only a small number of protocol deviations because the personnel involved in the study will receive intensive and continuous training and because the trial

will be closely monitored by trial investigators and periodically by a Data Monitoring Committee that will look at protocol deviations. Thus, the decrease in power due to exclusions of protocol deviations will be minimal. Table 1 shows that for the proposed sample size, the power is higher than the usually required 80%.

There may be deviations from the trial protocol if the baby's condition requires urgent action. In such situations the cord may be clamped and cut immediately after birth of the head and if the caregiver is involved in the resuscitation the timing of placental delivery may differ (this could be in either direction). We would expect this deviation to be equally distributed in the two groups. A second type of deviation could occur if a woman who has earlier given consent and randomly allocated to one group withdraws her consent after randomization. The withdrawal of consent after random allocation should be extremely rare since the random allocation will be made when vaginal delivery is imminent. We have looked at earlier trials where expectant management was used (because expectant management omits controlled cord traction) and did not find any suggestion that there was a compliance problem with omission of CCT. Nevertheless, the sample size calculation has a margin of additional power as mentioned in table 2 to ensure that such protocol deviations do not have a negative impact on the conclusions[17]

The actual management of third stage of labour will be recorded in all women to enable the analysis mentioned above.

Comparisons will be expressed as relative risks and risk differences with 95% confidence intervals. The analysis will be stratified by site, and if there is heterogeneity between the sites for any of the results possible causes of heterogeneity will be explored. In the presence of heterogeneity, the results will not be combined in a single summary estimate (or pooled estimate). In the absence of heterogeneity at the 5% level, the results will be combined.

The primary analysis will follow the following scheme for interpretation (Figure 1):[18] If the lower limit of the 95% confidence interval lies to the right of the non-inferiority

Table 2: CONSORT recommendations in the protocol – Checklist for non-inferiority and equivalence trials. Items 1 through 12[17]

Paper section and topic	Item	Descriptor	Reported on section
TITLE & ABSTRACT	1	How participants were allocated to interventions (e.g., "random allocation", "randomized", or "randomly assigned"), <i>specifying that the trial is a non-inferiority or equivalence trial.</i>	Title in cover page. Summary: section 1
INTRODUCTION Background	2	Scientific background and explanation of rationale, <i>including the rationale for using a non-inferiority or equivalence design.</i>	2 and 3. In particular, see 2.1.5, two last paragraphs for rationale for non-inferiority
METHODS Participants	3	Eligibility criteria for participants (<i>detailing whether participants in the non-inferiority or equivalence trial are similar to those in any trial(s) that established efficacy of the reference treatment</i>) and the settings and locations where the data were collected.	4.3 and 4.4.3
Interventions	4	Precise details of the interventions intended for each group <i>detailing whether the reference treatment in the non-inferiority or equivalence trial is identical (or very similar) to that in any trial(s) that established efficacy</i> , and how and when they were actually administered.	4.1
Objectives	5	Specific objectives and hypotheses, <i>including the hypothesis concerning non-inferiority or equivalence.</i>	3
Outcomes	6	Clearly defined primary and secondary outcome measures <i>detailing whether the outcomes in the non-inferiority or equivalence trial are identical (or very similar) to those in any trial(s) that established efficacy of the reference treatment</i> and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors).	4.2
Sample size	7	How sample size was determined <i>detailing whether it was calculated using a non-inferiority or equivalence criterion and specifying the margin of equivalence with the rationale for its choice.</i> When applicable, explanation of any interim analyses and stopping rules (<i>and whether related to a non-inferiority or equivalence hypothesis</i>).	4.4.3
Randomization – Sequence generation	8	Method used to generate the random allocation sequence, including details of any restrictions (e.g., blocking, stratification)	4.4.1
Randomization – Allocation concealment	9	Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	4.4.2
Randomization – Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	4.4.2
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.	4 (last sentence before 3.1)
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s), <i>specifying whether a one or two-sided confidence interval approach was used.</i> Methods for additional analyses, such as subgroup analyses and adjusted analyses.	4.4.3 & 4.5

margin (Δ) the experimental intervention will be declared "inferior" (situation H). Situations A-D indicate non-inferiority with respect to the pre-stated margin Δ . Situations E-G are inconclusive, although E and F are not likely to occur because the trial size guarantees sufficient power. If the results are inconclusive regarding the non-inferiority hypothesis and the whole 95% confidence interval lies to the right of zero (situation G), it will be concluded that the limited package was statistically significantly worse according to a superiority hypothesis.

Interim analysis

A Data Monitoring Committee (DMC) with no direct involvement in the trial will be appointed. The role of the DMC will be to deal with any ethical issues that may arise while the trial is in progress, and to scrutinize an interim analysis. An interim analysis will be conducted to be reviewed by the DMC after the completion of the first 5,000 participants. A second interim analysis will be conducted after 10,000 – 15,000 women are recruited. Interim analyses will be masked to trial investigators but not to DMC members. Reporting and handling of adverse events will be in accordance with the Good Clinical Practice guidelines.

Stopping the trial

The DMC will be asked to give advice regarding stopping the trial if they have proof beyond doubt of an important advantage or disadvantage for one of the treatment groups, and they consider that the results are likely to affect clinical practice. For the main outcome results of the interim analyses, the DMC will base their recommenda-

tion on a superiority hypothesis two-sided stopping rule: if one of the treatments is significantly superior to the other, they will consider to stop the trial. The Haybittle-Peto rule for the α -spending function will be used to determine the level of significance at the two interim analyses and at the final analysis.

Stratified analysis

It is likely that some centres will practice uterine massage and some not. A stratified analysis will be conducted of the primary outcome by the use of uterine massage, to assess the interaction of uterine massage by CCT. However, it is likely that such an analysis will be underpowered. The use of uterine massage will also be considered as a potential confounding variable.

Duration of the project

It is anticipated that the recruitment into the study in the centres can be completed in approximately 12 months. Recruitment will begin around November-December 2008 after trial procedures have been tested and materials have been procured and distributed to the study sites. (Calibrated drape BRASS-V and oxytocin).

Expected outcomes of the study

The main objective of this trial is to investigate whether a simplified package of third stage management can be recommended without increasing the risk of PPH. By avoiding the need for a manual procedure that requires training, the third stage management can be implemented in a more widespread and cost-effective way around the world even at the most peripheral levels of the health care system.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors contributed to the development of the trial protocol and approved the submitted manuscript. AMG is the guarantor of the manuscript

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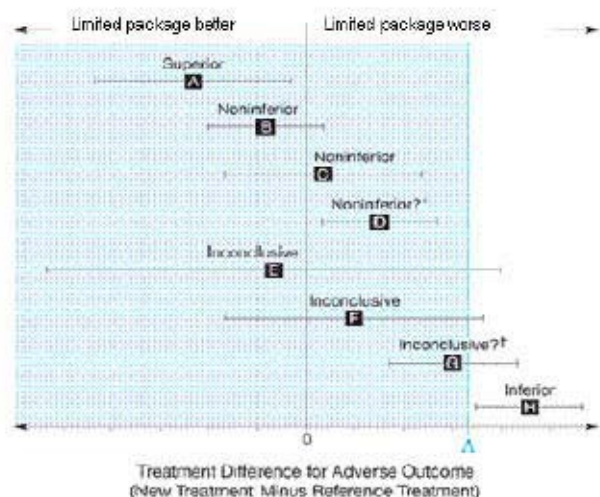


Figure 1
Scheme for the interpretation of the results of the primary analysis.

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Review

Interval debulking surgery for advanced epithelial ovarian cancer: A Cochrane systematic review

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Abstract

Objectives. To assess the effectiveness of interval debulking surgery (IDS) for patients with advanced stage epithelial ovarian cancer (EOC).

Methods. We searched the Cochrane Central Register of Controlled Trials, Medline, EMBASE, and reference lists for randomized controlled trials (RCTs) of advanced stage EOC. The trials had to report survival of women who had primary surgery and had IDS performed between cycles of chemotherapy comparing to survival of women who had conventional treatment (primary debulking surgery and adjuvant chemotherapy). Two review authors independently assessed trial quality and extracted data. Meta-analysis of overall survival (OS) and progression-free survival (PFS) was performed using fixed effects models.

Results. Three RCTs, involving 853 women of whom 781 were evaluated, met the inclusion criteria. OSs were substantial heterogeneity between trials ($I^2=58\%$). Subgroup analysis in two trials, wherein the primary surgery was not performed by the gynecologic oncologists, or was less extensive, showed benefit of IDS: hazard ratio=0.7 (95% confidence interval [CI]: 0.5 to 0.9, $I^2=0\%$). Substantial heterogeneity between two trials for PFS evaluating 702 women was also shown ($I^2=75\%$). Toxic reactions to chemotherapy were similar in both arms (RR=1.3, 95% CI: 0.4 to 3.6). Only one trial reported quality of life, which was generally similar in both treatment arms.

Conclusions. Our review could not conclude whether IDS would improve the survival of women with advanced EOC compared with conventional treatment. IDS appeared to yield benefit only in the patients whose primary surgery was not performed by expert surgeons.

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Keywords: Interval debulking surgery; Advanced epithelial ovarian cancer; Survival

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Introduction

A woman's risk of developing cancer of the ovaries by age 75 years varies between countries, ranging from 0.5% to 1.6% [1]. Primary surgery is the mainstay of treatment for ovarian cancer, followed by adjuvant chemotherapy if indicated. The aim of primary surgery is to remove as much tumor as possible because the amount of residual tumor is one of the most important prognostic factors for survival of women with epithelial ovarian cancer (EOC) [2–4]. An optimal surgery, which is usually defined as a removal of tumors to <1–2 cm, is not always possible especially when the patients have poor medical condition precluding prolonged surgery or when the diseases are extensive. After suboptimal surgery (residual tumors >1–2 cm), induction chemotherapy to reduce tumor size before considering secondary surgery can play an alternative role. In the circumstances when primary debulking surgery is not possible (or not being attempted at all) with only biopsy done for diagnostic purpose, the term neoadjuvant chemotherapy (NAC) is more specifically used to describe the administration of chemotherapy prior to the primary debulking surgery. When a few cycles of chemotherapy are administered with some tumor response, secondary surgery or so called interval debulking surgery (IDS) between the courses of chemotherapy may be possible. The IDS is usually performed after 2 to 4 cycles of chemotherapy because more cycles of chemotherapy could result in the chemotherapy selectively destroying chemotherapy sensitive tumor cells leaving more of the chemotherapy resistant clones.

Many retrospective studies or prospective non-randomized trials reported the beneficial effect of chemotherapy after inoperable advanced EOC or those with gross residual diseases that it may increase the number of patients suitable for secondary surgery (IDS). The rates of optimal resection in IDS after chemotherapy were reported ranging from 77% to 94% [5]–[13]. Other potential benefits of IDS after chemotherapy compared to aggressive primary debulking surgery were also demonstrated, such as, lesser blood loss, lower requirement of intensive care unit admission and duration of hospital stay due to the tumors being smaller [7,11,12]. IDS, by removing the smaller tumor masses induced by chemotherapy, would certainly facilitate the response of any residual tumors to subsequent chemotherapy. The quality of life (QOL) of patients treated with IDS was also reported in one study to be better than those who had conventional treatment (primary debulking surgery followed by a complete and continual cycles of adjuvant chemotherapy) [6].

Unlike the aforementioned advantages of IDS, there is still conflicting evidence regarding its survival benefit in comparison to conventional treatment. Many studies [10,12–17] showed similar survival rates of patients who had IDS after few cycles of chemotherapy and those who had conventional treatment. Only few studies reported significantly longer survival of patients having IDS [8,18], and even fewer studies showed an inferior result of IDS than optimal primary cytoreduction [19]. Of noted, most studies of IDS were non-randomized or retrospective in nature with various character-

istics of the patients and their diseases e.g. extent of residual tumor after primary surgery or IDS, tumor response after induction chemotherapy and prior to IDS, etc. [8,10,18–20]. These factors may lead to conflicting results on the survival benefit of IDS. Even among a few randomized controlled trials (RCTs) [21–23] which evaluated the role of IDS in EOC, their findings did not agree on the benefit of IDS on the patients' survival outcomes. Two trials [21,23] showed similar survival rates of patients between the IDS and conventional treatment, while the other [22] showed significantly longer survival in the IDS group which was still present after a 10-year follow-up [24].

Along with many studies on the role of NAC/IDS, many review articles have also been published. Focusing on the evidenced-based reviews which addressed the specific question whether the advanced EOC patients should have surgery before (conventional treatment) or after few cycles of chemotherapy (NAC/IDS), we could identify only one meta-analytical study [25] and two systematic reviews [26,27]. The meta-analytical study reviewed the role of platinum-based NAC/IDS for advanced EOC, involving 835 patients from 51 studies [25]. The result showed that survival of patients who had NAC/IDS was inferior to those who had primary surgery. However, this review included only phase I–II and retrospective studies. The other systematic review included three RCTs and 32 non-randomized or retrospective studies [26]. The results from these studies were simply described and tabulated according to the survival outcomes of the patients in the NAC/IDS compared to the conventional arm. However, there was no survival meta-analysis. The last systematic review [27], by the Cochrane Collaboration Group, could identify only one RCT [28] which found no significant survival difference of patients who were treated with either treatment. To be noted, the objective of these three systematic reviews was to evaluate if NAC could be used in lieu of primary surgery, rather than the role of repeated surgery or IDS after a primary surgery. We found only one previous meta-analytical study which specifically reviewed the role of IDS in advanced EOC [29]. The authors identified 33 publications and included three RCTs and three historical cohort trials in their review [29]. Homogeneity testing was not statistically significant by the Breslow–Day method. Significant survival benefit from the IDS was identified by the Mantel–Haenszel method with odds ratio of 0.5 ($p=0.02$) [29].

Because of potential intrinsic biases in many retrospective or phase I/II studies, together with conflicting data from the RCTs, a definite conclusion about the advantage of IDS after a suboptimal primary surgery could not be made. We conducted a thorough systematic review focusing only to the high quality data from RCTs to assess the effectiveness and complications of IDS for patients with advanced stage EOC.

Materials and methods

Electronic databases from January 1966 to June 2008 including Medline, EMBASE using Ovid, and the Cochrane Central Register of Controlled Trials (CENTRAL), trials registered, and reference lists of journals relevant to the subject

were searched for RCTs involving patients with advanced stage EOC. The patients must have histological confirmed diagnoses from primary surgery which may range from tumor biopsy, tumor removal, or standard surgical staging for EOC.

Eligible RCTs had to compare the survival of patients who were randomized to have IDS performed after 2 to 4 cycles of NAC or induction chemotherapy, followed by further chemotherapy with that of the patients who had only adjuvant chemotherapy without IDS. Phase II study and retrospective analyses or case series were not included.

The keywords used for the literature search included: ovarian cancer or neoplasm, (neoadjuvant or induction or preoperative) chemotherapy, interval debulking or secondary surgery. Two review authors (ST and SM) independently examined all the titles and abstracts retrieved by electronic searching, independently assessed full texts of potentially relevant trials, and extracted data from the eligible trials.

Numbers and characteristics of patients in the included trials, detail of surgical interventions including expertise of surgeons, detail of chemotherapy treatment, and length of follow up were extracted from individual included trials. We abstracted the log hazard ratio (HR) and its variance as data for overall survival (OS) and progression-free survival (PFS). If HRs were adjusted for prognostic factors, these were extracted in preference to unadjusted HRs. We estimated HRs using Parmar's methods [30] from the included trial which reported only Kaplan–Meier survival curves. The data of log HRs of overall death, disease progression and risk ratios of toxic reactions to chemotherapy

were combined using fixed effect model in the RevMan software. Where possible, all data abstracted were those relevant to an intention to treat analysis.

Results

The search identified 134 references whose titles and abstracts were examined. Seventeen studies were potentially relevant to this review. Two studies [31–33] could be readily excluded from the abstracts' data (one of which was presented as abstracts from two proceeding conferences of the American Society Clinical Oncology annual meetings). Full text articles of 15 studies were obtained and were assessed for eligibility. Twelve studies were additionally excluded. We present reasons for individual excluded trial in Table 1 [6–9,28,31,33–40].

Three RCTs met all inclusion criteria and were included in this review involving 853 randomized women [21–23]. They were multicenter trials: one from United Kingdom involved four institutions which were the referral centers for cancer care [21]; one by the European Organisation for Research and Treatment of Cancer (EORTC) involved 14 participating institutions in Europe [22]; and the last one by the Gynecologic Oncology Group (GOG) from the United States involved more than 42 cancer centers [23].

Median lengths of follow-up were reported: 48 months in the trial of Redman [21], 42 months in the EORTC [22] and 47 months in the GOG trials [23]. Although van de Burg et al. from the EORTC trial presented their long term follow-up

Table 1
Characteristics of excluded studies

Study, year [reference]	Type of study	Reason for exclusion
Evdokimova, 1982 [33]	RCT	Patients without ascites were selected to have conventional treatment while those with ascites had either NAC/IDS or conventional treatment.
Liu, 2004 [28]	RCT	NAC given only for 1 cycle via intra-arterial route before IDS in the study arm.
Park Simon, 2006 [34]	RCT	NAC given randomly to the patient for either 2 versus 3 cycles, followed by IDS in both arms.
Kumar, 2007 [31]	RCT	Histopathology of ovarian cancer not required.
Dutta, 2005 [35]	RCT	Preclinical study for proapoptotic and antiapoptotic proteins in ovarian cancer. No survival outcome evaluation.
Fuso, 2006 [36]	Controlled clinical trial	NAC/IDS was selectively assigned to the patients who were judged to be inoperable.
Kuhn, 2001 [8]	Controlled clinical trial	NAC/IDS was selectively assigned to the patients who were in poor general health for primary surgery while the patients who did not agree for IDS or had psychologic reasons were assigned to the control group.
Angioli, 2006 [37]	Controlled clinical trial	NAC/IDS was selectively assigned to the patients who were determined to be inoperable (based on laparoscopic findings).
Giannopoulos, 2006 [7]	Controlled clinical trial	NAC/IDS was selectively assigned to the patients who deemed inoperable from CT scan and initial laparoscopy. Histopathology of ovarian cancer not required.
Lee, 2006 [9]	Controlled clinical trial	NAC/IDS was selectively assigned to the patients who agreed to undergo the protocol. NAC ranged from 3 cycles to 6 cycles. Some patients had secondary surgery which was not an interval setting.
Solomon, 1988 [38]	Prospective study	IDS was selectively performed only in the patients who had not been debulked at primary surgery. Second-look surgery was also performed in patients with clinical complete remission.
Recchia, 2001 [39]	Prospective study	No control group. Histopathologic diagnosis of ovarian cancer was not required.
Chan, 2003 [6]	Prospective study	No control group. Patients were selected by their inoperability based on CT scan without an attempt of primary operation. Histology for a pathologic diagnosis of ovarian cancer was not required.
Ikeba, 2004 [40]	Prospective study	No control group.

Abbreviations: IDS, interval debulking surgery; NAC, neoadjuvant chemotherapy; RCT, randomized controlled trial.

(10 years) as an oral presentation in the European Society of Gynaecological Oncology annual meeting in 2005 [22], sufficient data was not available for meta-analysis.

Some characteristic differences of the patients, their diseases, and interventions among the three trials were observed e.g. the expertise of the primary surgeons; the definitions of optimal debulking from primary surgery, as having residual diseases <2 cm [21] or <1 cm [22,23]; timing of randomization [21–23]; type of chemotherapy in each trial; response rates to induction chemotherapy before the IDS; and etc. Table 2 provided some characteristic descriptions of the included trials.

All three trials reported HRs for OS [21–23] which was calculated either from the initiation date of induction chemotherapy [22], date of randomization after primary surgery and before chemotherapy [21] or after three cycles of

chemotherapy [23]. Both the GOG and the EORTC trials [22,23] reported HRs adjusted for prognostic factors of age, performance status, stage, tumor grade, response to induction chemotherapy, number of lesions, ascites, and size of residual diseases at three time points: after primary surgery, before and after IDS while the Redman trial reported unadjusted HRs. From the three included trials, 853 women were randomized and 781 women (91.5%) were followed up. We found heterogeneity of the HRs of all deaths among the trials ($I^2=58\%$). We explored the sources of heterogeneity by performing subgroup meta-analysis for OS according to expertise of surgeons. In the two trials wherein the primary surgery was performed by general surgeons [21,22], the IDS showed marginally significant survival benefit: hazard ratio comparing the risk of death in the IDS and chemotherapy only

Table 2
Characteristic of included studies

Study, year [reference]	Redman, 1994 [21]	van De Burg, 1995 (EORTC trial) [22]	Rose, 2006 (GOG trial) [23]
Study duration	04/1986–02/1990	03/1987–05/1993	06/1994–01/2001
Timing of randomization	Randomized at entry (after primary surgery)	Randomized after 3 cycles of chemotherapy	Randomized after 3 cycles of chemotherapy
Method of randomization	Random permuted blocks method	Random at Central EORTC data center	Randomly permuted blocks in a blind fashion
Number randomized	86	319	448
Number evaluable	79	278	424
Surgery	Primary surgery must be performed with a maximal attempt to remove tumors. (only 9% were gynecologic oncologists)	Primary surgery were performed in various referring hospitals. (the levels of surgeons not specified)	95% of primary surgery were performed by gynecologic oncologists aiming to remove tumors as much as possible
Participants	Stage II–IV (only resectable stage IV) PS ECOG: at least 2 Histology proven RD>2 cm IDS performed only in patients who had no evidences of PD, and no extraperitoneal tumor>1 cm	Stage IIB–IV Age<75 with performance status WHO: 0–2 Histology proven (central pathologic review) RD>1 cm Randomized only the patients who had no PD and no contraindication to surgery	Stage III–IV ^a Age<75 with performance status ACOG: 0–2 Histology proven (central pathologic review) RD>1 cm Randomized only the patients who had no PD, no extraperitoneal tumor>1 cm, and no medical contraindication
Interventions	Arm 1: IDS after sufficient tumor response in between the 8 cycles of tri-weekly of PC or PAB followed by cyclophosphamide up to 5 cycles Arm 2: No IDS (the same regimen of chemotherapy)	Arm 1: IDS after 3 cycles of tri-weekly PC, followed by 3 more cycles of PC Arm 2: No IDS (the same regimen of chemotherapy).	Arm 1: IDS after 3 cycles of tri-weekly PT, followed by 3 more cycles of PT Arm 2: No IDS (the same regimen of chemotherapy).
Outcomes of interest	OS Peri-operative complications	OS, PFS Peri-operative complications	OS, PFS Adverse effects Quality of life
Response evaluation	PE, imaging studies (CA 125 not used)	PE, imaging studies, and CA 125 (WHO response criteria)	PE, imaging studies, and CA 125 (PD=an increased CA 125>100 U/ml or doubling of the nadir)
Survival evaluation	OS measured from the date of entry (date of randomization)	OS measured from the date of entry (date when chemotherapy begun)	OS and PFS measured from the date of randomization (after 3 cycles of chemotherapy)
Notes	–	Consolidation chemotherapy allowed	Consolidation chemotherapy allowed

Note: All the three trials were multi-center randomized control trials with intention-to-treat analysis.

Abbreviations: ECOG, Eastern Collaborative Oncology Group; PAB, cisplatin/adriamycin/bleomycin; PC, cisplatin/cyclophosphamide; PD, progressive disease; PE, physical examination; PFS, progression-free survival; PS, performance status; PT, paclitaxel/cisplatin; OS, overall survival; RD, residual disease; WHO, World Health Organization.

^a The Gynecologic Oncology Group trial by Rose et al. excluded patients with stage IV diseases after March 1996 when the European Organization for Research and treatment of Cancer trial by van Der Burg et al. reported a greater benefit from secondary surgery after the exclusion of such patients from the analyses.

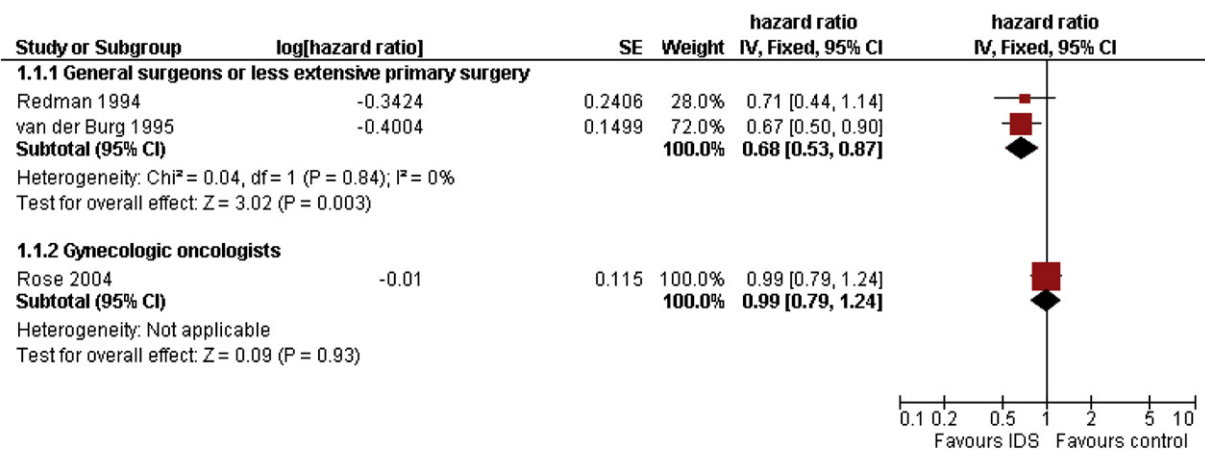


Fig. 1. Overall survival of epithelial ovarian cancer patients who had interval debulking surgery and those who had only chemotherapy after primary surgery according to the expertise of surgeons or the extent of primary surgery.

arms was 0.7 (95% CI: 0.5 to 0.9). Results of subgroup meta-analyses for all deaths are presented in the Fig. 1.

For PFS, only two RCTs [22,23] had available data: one trial reported HR, adjusted for prognostic factors [23] while the other presented Kaplan–Meier disease-free survival curves [22], from which we used Parmar's method to estimate the HR. The two trials were included in the meta-analysis [22,23] involving 767 randomized women of whom 702 were followed up. The HRs comparing the risk of progression-free survival in the IDS with chemotherapy only arms again showed substantial heterogeneity between trials ($I^2 = 75\%$).

Toxic reaction was reported in both treatment groups in the Redman [21] and EORTC [22] trials, and was the only adverse event possible to meta-analyse. The pooled relative risk of toxic reactions to chemotherapy using Mantel–Haenszel methods comparing rates of toxic reactions to chemotherapy in the IDS with chemotherapy-only arms was 1.2 (95% CI: 0.4 to 3.6) (Fig. 2). The GOG trial [23] reported that rates of other adverse events were similar in the two groups, except for a significant higher rate of neurological adverse events in the chemotherapy-alone group (26% versus 16%; $p = 0.01$).

QOL was assessed only in the GOG trial and the results were subsequently reported by Wenzel et al. [41]. The self-reported QOL was assessed in four settings, according to the Functional Assessment of Cancer Therapy-Ovarian (FACT-O), version 2-questionnaire. The evaluations were at baseline before allocation to IDS or chemotherapy only, at the sixth cycle of

chemotherapy, at 6 and 12 months after starting treatment. Completion rates for these questionnaires declined from 90% for the first questionnaire to 83%, 83%, and 80% for the subsequent questionnaires respectively. Nevertheless, lower completion rates were noted in the IDS group compared to chemotherapy only group especially at the second assessment, 77% and 89% respectively ($p < 0.001$). At 6 months after starting treatment, significantly more patients who had only chemotherapy experienced persistent numbness or tingling than those who had IDS, 54% versus 38% ($p = 0.012$). Otherwise, QOL was not significantly different in the two treatment groups at any time point.

Discussion

Our systematic review included three RCTs, which evaluated 781 patients out of 853 randomized. The results provided inconclusive evidence whether IDS improves or worsens the OS and PFS of the patients. Potential reasons for the inconclusive evidence are explored. Firstly, the small number of included studies, evaluating 781 patients, 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 may be the expertise or the maximal effort to do the primary debulking surgery of the surgeons in the participating institutions of each study.

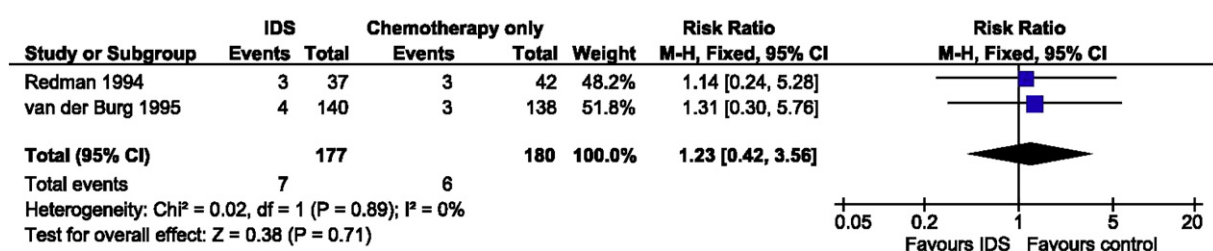


Fig. 2. Toxic reaction to chemotherapy in the epithelial ovarian cancer patients who had interval debulking surgery and those who had only chemotherapy after primary surgery.

Majority or 99% of the operations in the GOG trial were performed by the gynecologic oncologists or fellowship-trained in various cancer centers [23] while the procedures in the Redman trial were performed mostly by general surgeons or gynecologists (only 9% by gynecologic oncologists) in various hospitals [21] or in the EORTC trial in which the primary surgery was performed in various hospitals in Europe wherein the expertise of surgeons was not specified [22] but the maximal effort to perform primary surgery was not attempted in all patients with different extent of debulking surgery [42,43]. Since there is substantial evidence from many retrospective studies that the extent of optimal surgery affects the survival of patients with EOC [2–4], the maximal primary surgical efforts in the optimal surgical setting in the GOG trial might indicate that their primary surgery was sufficient, that another subsequent surgical attempt would not affect the survival further. In comparison to the Redman and EORTC trials [21,22] in which the primary surgery were carried out in suboptimal settings when most of the operations were not performed by gynecologic oncologists [21] or not in the maximal attempt (with less extent of primary debulking surgery) resulting in high proportion of large residual tumors [42,43], so the IDS which were performed after the tumors were down-sized by chemotherapy appeared worthwhile (although significant only in the EORTC trial). Our subgroup meta-analysis confirmed this proposal that IDS had benefit in this particular subgroup of patients. Nevertheless, this should be interpreted with caution because our subgroup analysis was based on only two trials [21,22].

The second difference between these trials was the timing of randomization. Redman was the only trial which randomized the patients into two groups (to have or not to have IDS) at the start of trial [21]. Only 67% of patients in the IDS group of this study actually had it because the other assigned patients had diseases progression or deaths precluding the IDS. While the other two trials of GOG and EORTC randomized only the patients who showed some response to induction chemotherapy [22,23]: this resulted in a high percentage of the patients (approximately 93% in both trials) who were randomized to undergo IDS really had it. This difference may affect the result from each trial, based on the design of an intention to treat analysis in all of these trials.

We also explored the patients or their disease characteristic as the other potential reason for different effects of IDS on survival outcomes. Two trials of Redman and the GOG did not show any advantage of IDS [21,23] while the EORTC demonstrated significant survival improvement with IDS [22]. Redman trial included only 79 patients for analysis of OS, and therefore did not have much influence on the results of the meta-analysis [21]. The difference in outcomes from the GOG [23] and EORTC [22] trials may be due to the different proportions of patients who had poor response to induction chemotherapy: approximately 52% of patients in GOG trial had residual diseases of >1 cm after induction chemotherapy [23] compared to 44% in the EORTC trial [22]. This might be interpreted that the GOG trial had a higher proportion of patients who had more aggressive tumors (who generally had poorer prognosis than

those who showed some response), and so would not have a survival benefit from any treatment, even the optimal IDS. However, this mechanism of tumor aggressiveness and prognosis may not solely explain the ultimate outcome of the patients because the patients in the EORTC trial [22] who had tumor >1 cm after induction chemotherapy but were removed to <1 cm had better survival benefit than any other group of women in the trial. This might suggest that the IDS may play some role in survival improvement.

To emphasize on the importance of the sensitivity or response to chemotherapy before IDS, we would like to point out the findings from the GOG and EORTC trials which showed that the patients whose tumor masses were reduced by chemotherapy to <1 cm before the IDS [22,23] had superior survival than the other groups. This response to chemotherapy might be used as a selective criterion for the patients who are likely to gain survival benefit from IDS.

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 [23]. However, this adverse effect may be related to a particular drug and might not be experienced in the other settings using other chemotherapeutic regimens.

For the QOL comparison, which was assessed only in the GOG trial [41], patients in the chemotherapy only arm had a higher rate of neurotoxicity than those in the IDS arm despite a similar total dose of chemotherapy exposures. The authors ascribed this finding to intermission from chemotherapy exposure allowing 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 patients at every time point of assessment, definitive conclusions cannot be made because a significantly lower proportion of patients in the IDS group completed the 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.

Three major studies are ongoing aiming to address the question whether NAC before the surgery could replace the primary surgery before adjuvant chemotherapy in terms of survival comparison [44–46]. The three trials by the Royal College of Obstetrician and Gynaecologist in United Kingdom (CHORUS study) [44], the EORTC in Europe (EORTC 55971 study) [45], and the Japan Clinical Oncology Group in Japan (JCOG 0602) [46] are designed in the same approach that the patients in the NAC arm would have IDS (which is actually the first or primary surgery) before further chemotherapy while the patients in the other arm would have conventional treatment. However, the patients in the conventional arm may also have IDS upon discretion of the physician. Hence, these studies would not be able to answer the actual role of IDS. To directly address the definite role of IDS, future studies should focus on a comparison of current conventional primary surgery with adjuvant chemotherapy versus NAC without any attempt to remove the bulk of tumors (except a biopsy for histologic

diagnosis) followed by IDS (which should be allowed only in this arm) and then by further chemotherapy.

Conclusions

The heterogeneity of the results in our review precludes any definitive suggestion for clinical practice. The choice to perform IDS after chemotherapy must be individualized. Since we found the benefit of IDS in the subgroup of patients whose primary surgery has not been performed under the optimum condition e.g. by the oncologic surgeons or with the maximal surgical effort, we would like to make a comment that the IDS may improve the patient's survival in these settings.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Acknowledgments

This review is modified from the systematic review and meta-analysis of "Interval debulking surgery for advanced epithelial ovarian cancer" first published as a Cochrane Review in The Cochrane Library 2008 issue [47]. The main findings and the core issues are the same as the original Cochrane Review except for some ongoing studies which were additionally reviewed here. Cochrane Reviews are regularly updated as new evidence emerges and in response to comments and criticisms, and The Cochrane Library should be consulted for the most recent version of the Review.

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One-Day Compared With 7-Day Nitrofurantoin for Asymptomatic Bacteriuria in Pregnancy

A Randomized Controlled Trial

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OBJECTIVE: To evaluate whether a 1-day nitrofurantoin regimen is as effective as a 7-day regimen in eradicating asymptomatic bacteriuria during pregnancy.

See related article on page 346.

*For a list of members of the World Health Organization Asymptomatic Bacteriuria trial group who participated in this study, see the Appendix online at <http://links.lww.com/A644>.

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METHODS: A multicenter, double-blind, randomized, placebo controlled noninferiority trial was conducted in antenatal clinics in Thailand, the Philippines, Vietnam, and Argentina. Pregnant women seeking antenatal care between March 2004 and March 2007 who met the inclusion and exclusion criteria were invited to participate in the study. Those who consented were randomly allocated to receive either a 1-day or a 7-day course of 100 mg capsules of nitrofurantoin, which was taken twice daily. The primary outcome was bacteriologic cure on day 14 of treatment.

RESULTS: A total of 1,248 of 24,430 eligible women had asymptomatic bacteriuria, making the overall prevalence of 5.1%. Of these 1,248 women, 778 women were successfully recruited, and 386 and 392 women were randomly allocated to 1-day and 7-day regimens, respectively. *Escherichia coli* was the most common potentially pathogenic bacteria detected, its prevalence approaching 50%. Bacteriologic cure rates at treatment day 14 were 75.7% and 86.2% for 1-day and 7-day regimens, respectively. The cure rate difference was -10.5% (95% confidence interval -16.1% to -4.9%). Mean birth weight and mean gestational age at delivery were significantly lower in the 1-day regimen group. There were fewer adverse effects in the 1-day regimen group, but the differences were not statistically significant.

CONCLUSION: A 1-day regimen of nitrofurantoin is significantly less effective than a 7-day regimen. Women with asymptomatic bacteriuria in pregnancy should receive the standard 7-day regimen.

CLINICAL TRIAL REGISTRATION: ISRCTN, isrctn.org, ISRCTN11966080

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LEVEL OF EVIDENCE: I



The prevalence of asymptomatic bacteriuria in pregnancy ranges from 2–11%, similar to data in nonpregnant populations. However, whereas asymptomatic bacteriuria is relatively benign in nonpregnant populations, 20–30% of culture-positive pregnant women if untreated develop symptomatic disease, often pyelonephritis and its complications.^{1–3} There is also evidence of increases in both low birth weight and preterm delivery and in the subsequent development of preeclampsia if pregnant women with asymptomatic bacteriuria are not treated.⁴ Thus, many authorities recommend screening all pregnant women for asymptomatic bacteriuria and treating those with evidence of infection.⁵ In this respect, antibiotic treatment has been demonstrated to be effective in reducing the risk of subsequent pyelonephritis in women with asymptomatic bacteriuria in pregnancy.⁶ However, achieving this level of care may be elusive, especially in developing nations.

A Cochrane review updated in October 2006 assessed the efficacy of length of treatment on eradicating asymptomatic bacteriuria in pregnancy. The authors concluded that there was insufficient evidence to evaluate whether 1-day therapy with an antibiotic or treatment for a longer duration (traditionally 7 days) had similar efficacy in eradication asymptomatic bacteriuria of pregnancy.⁷

Antibiotics used to treat asymptomatic bacteriuria in pregnancy include ampicillin, amoxicillin, trimethoprim-sulfamethoxazole, cephalexin, and nitrofurantoin. However, resistance of *Escherichia coli* and other uropathogens to ampicillin, trimethoprim-sulfamethoxazole, and first-generation cephalosporins has been steadily increasing, currently approaching 40%.⁸ Fortunately, little or no changes in bacterial resistance to nitrofurantoin have been noted.⁹ We designed a World Health Organization (WHO) multicenter trial to compare whether a 1-day treatment with nitrofurantoin (100 mg twice per day) is as effective as a 7-day regimen (100 mg twice per day) in eradicating asymptomatic bacteriuria during pregnancy.

MATERIALS AND METHODS

A hospital-based, multicenter, double-blind, placebo-controlled, randomized controlled trial was conducted in antenatal clinics in Thailand, the Philippines, Viet Nam, and Argentina. Participating centers were Maharaj Nakorn Chiang Mai Hospital (Chiang Mai University), King Chulalongkorn Memorial Hospital (Chulalongkorn University), Songklanagarind Hospital (Prince of Songkla University) and Srinagarind Hospital (Khon Kaen University) in Thailand; Centro Rosarino de Estudios Perinatales, in Rosario,

Argentina; National Hospital for Obstetrics and Gynecology, Hanoi, in Viet Nam; and Philippines General Hospital (University of the Philippines), Manila, in the Philippines. All these centers are part of the WHO Maternal and Perinatal Research Network, each having extensive trial experience. This network involves centers throughout the world from both developed and developing countries.

Pregnant women seeking antenatal care visits at the participating centers between March 2004 and March 2007 and capable of giving informed consent were recruited at gestational ages between 12 weeks and 32 weeks. Eligibility was asymptomatic bacteriuria with the microorganism sensitive to nitrofurantoin, plus absence of symptoms suggesting urinary tract infection (UTI), no history of treatment for UTI during the current pregnancy, presence of an underlying disease that required continuous steroids and/or antibiotic treatment, antibiotic hypersensitivity, or any hematologic disease including glucose-6-phosphate dehydrogenase (G6PD) deficiency. An additional exclusion criteria required by the Argentinean Center was the ineligibility of women with asymptomatic bacteriuria, due to *Streptococcus* Group B, where a specific antibiotic treatment regimen was required.

Instructions (written and oral) were provided by trained research assistants at each participating center and included how to appropriately collect midstream urine samples into sterile containers. After collection, a microbiologist or a trained research assistant tested the urine sample with Orion Diagnostica's Uricult dipslide (Orion Diagnostica Oy, Espoo, Finland), incubating the dipslide at 35°C to 37°C for 24 hours while the remainder of the sample was refrigerated. Dipslide culture was chosen because it provides results comparable to standard loop inoculation methods.¹⁰ We also evaluated the diagnostic performance of the dipslide, comparing it with urine culture using the data from Argentina, where all pregnant women had standard urine culture performed.¹¹ The dipslide was evaluated by the microbiologist the following day. If the results were positive (100,000 or more colony-forming units per milliliter), the pathologic findings were corroborated by plating a sample from refrigerated urine on both Blood and MacConkey agar plates, the colonies isolated tested for antibiotic susceptibility. These women were then formally diagnosed as having asymptomatic bacteriuria, became eligible for random assignment. All participating microbiologists were trained in the dipslide technique, and their laboratories were routinely audited. Note that glucose-6 phosphate dehydrogenase (G6PD)



deficiency is relatively common in Southeast Asia, particularly in Thailand, where the reported prevalence is 11.1% in male and 5.8% in female cord blood samples.¹²

Recruited women with asymptomatic bacteriuria were screened (Berstein assay) for glucose-6 phosphate dehydrogenase deficiency before receiving any treatment and were excluded from randomization if positive. Before implementing this assay all laboratories were trained and certified for the assay.

Culture-positive women without G6PD deficiency who consented were randomly allocated to receive either 1-day, (intervention group) or 7-day (control group) course of 100-mg capsules of nitrofurantoin to be taken twice daily. Women in the intervention group received a treatment package containing two 100-mg nitrofurantoin capsules for day 1 and 12 of identical placebo, all capsules to be taken, orally, twice daily with food. Women in the control group received an identical treatment package in which all fourteen capsules contained 100-mg nitrofurantoin to be taken twice daily for 7 days. All participants were requested to return to antenatal care clinic 14 days later, at which time a dipslide and regular urine culture were repeated and compliance determined by recording the number of the capsules remaining in the treatment box. Adverse effects, identified through interviews, were recorded on standard forms. Additional therapy, if required, was dictated by the new culture and sensitivity results, treatment continuing until cultures were negative. All participating women received standard antenatal care provided by the clinics, and their clinical courses were monitored until delivery to assess for pyelonephritis, preterm delivery, and low birth weight.

Randomization codes were conducted independently for each study site by the statistical unit at the Department of Reproductive Health and Research, the World Health Organization, Geneva, Switzerland. The random allocation sequence was generated using computer-generated random numbers with randomly varying blocks of 6–8 (SAS software, SAS Institute, Inc., Cary, NC). The random allocation was concealed by using sealed, opaque treatment boxes numbering sequentially using the sequence described above.

The primary maternal outcome was bacteriologic cure after antibiotic treatment, which was assessed by a urine culture 14 days after the initiation of treatment. Secondary outcomes included the incidences of symptomatic UTI, preterm delivery, and adverse effects. The neonatal outcomes were low birth weight and congenital malformations. Pyelonephritis was diagnosed when systemic symptoms or signs such as

fever, chills, nausea, vomiting, and flank pain occurred in the presence of bacteriuria. Symptoms of lower tract infection (ie, frequency and dysuria) might or might not be present.¹³ Preterm delivery was documented when delivery occurred before 37 completed weeks.¹⁴ Low birth weight was defined as birth weight less than 2,500 g.¹⁴

Sample size was calculated for the primary outcome. Considering this trial as an equivalence one, we estimated that regimens would be 80% effective. At 95% confidence level and a power of 90%, an acceptable margin of noninferiority in effectiveness of treatment was 7.5%, for a one-tailed test. The required number of women per treatment group and the number of women to be screened (based on 5% prevalence) were 446 and 17,840, respectively.¹⁵ We chose to use a one-tailed test because we want to confirm that a 1-day regimen of nitrofurantoin is not inferior to the 7-day regimen. A sample size of screening 18,000 pregnant women was planned.

All centers adhered to the standardized trial procedures, including the use of data collection forms. Completed data collection forms from all participating hospitals except CREP, Rosario, Argentina were sent to Khon Kaen University monthly; data entry and audit were performed continuously. All data were entered and cleaned and queries checked immediately with the local investigators. At CREP, data entry and audit were also performed continuously and update databases were sent to Khon Kaen University every three months.

Descriptive statistics were used to describe characteristics of the participants in each arm. The results were reported as intention to treat and with comparisons between 1-day and 7-day regimens of nitrofurantoin treatment. Relative risk (RR) (or cure rate ratio) and risk difference with 95% confidence intervals (CIs) were used to compare the differences of categorical outcomes. Mean differences with 95% CI were used for continuous outcomes. The trial was approved by the Scientific and Ethical Review Group of the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, the WHO Ethics Review Committee and the institutional review boards of the participating centers.

RESULTS

A total of 25,326 women were screened, of whom 24,430 were eligible. There were 1,827 women with positive dipslide for whom urine culture confirmation was sought. Of these women's cultures, 1,248 returned positive, giving the overall prevalence of 5.1%.



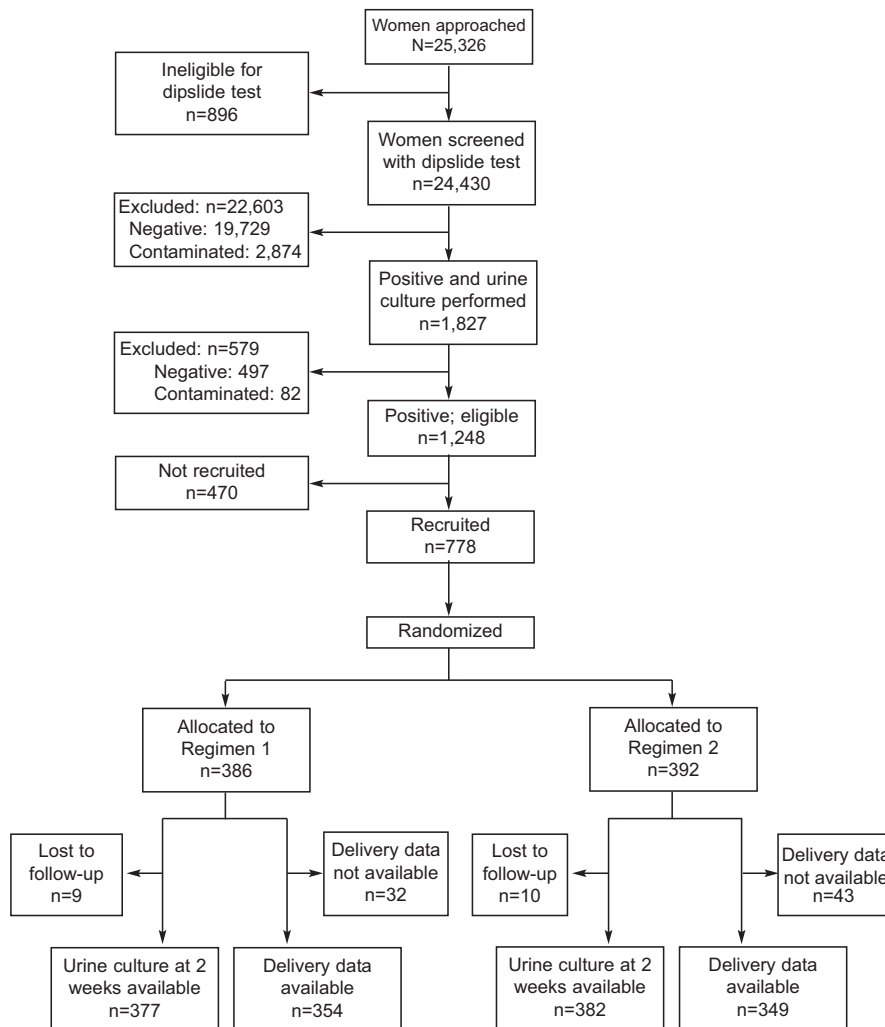


Fig. 1. Trial profile.

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However, only 778 of 1,248 women were recruited into the trial. Main reasons for failure to recruit eligible women included nitrofurantoin resistance (32.2%), loss to follow-up before recruitment could be initiated (22.9%), failure to be in a gestational age range of 12–32 weeks (12.5%), presence of G6PD deficiency or the screening result was unavailable (11.2%), and ineligibility criteria discovered only after the culture had been performed (10.6%). The prevalence of G6PD deficiency among women with positive urine culture was approximately 4%.

We allocated 386 and 392 women to 1-day and 7-day regimens, respectively. Three hundred seventy-seven (97.7%) women in the 1-day regimen group and 382 (97.4%) women in the 7-day regimen group returned for their 2-week follow-up urine culture. Delivery outcomes were available in 354 (91.7%) and 349 (89.0%) women in the 1-day and 7-day regimen group, respectively (Fig. 1).

The sociodemographic characteristics of each group including age, gravidity, and parity were very similar at entry. Compliance was both similar and excellent; 98% of the women in both groups ingested all their tablets (Table 1).

Table 1. Characteristics of Women at Recruitment by Regimen of Nitrofurantoin

Characteristics	1-Day Regimen	7-Day Regimen
Age (y)	386, 27.0 (± 5.9)	392, 26.9 (± 5.7)
School attendance (y)	385, 12 (0–22)	391, 12 (0–19)
Gravidity	386, 2 (1–8)	392, 2 (1–14)
Parity	386, 0 (0–8)	392, 0 (0–11)
Time from enrolment to follow-up (wk)	377, 2 (0–22)	385, 2 (1–15)
Women taking any other medications/supplements	214 (55.4)	205 (52.3)

Data are sample n, (%), mean ($\pm$ standard deviation), or median (range).



Table 2. Causative Agents of Asymptomatic Bacteria Among Pregnant Women With Positive Urine Culture at Recruitment by Treatment Regimen

Microorganisms	1-day Regimen	7-day Regimen
<i>Escherichia coli</i>	47.6 (186)	43.2 (172)
Klebsiella species	4.3 (17)	5.8 (23)
Enterobacter species	5.1 (20)	3.3 (13)
<i>Staphylococcus saprophyticus</i>	12.3 (48)	12.8 (51)
<i>Streptococcus</i> Group B	8.2 (32)	7.0 (28)
Enterococcus species	9.2 (36)	14.3 (57)
<i>Staphylococcus aureus</i>	6.4 (25)	8.0 (32)
<i>Staphylococcus</i> -ve	3.6 (14)	2.8 (11)
<i>Proteus</i>	0.3 (1)	0.3 (1)
Others	3.1 (12)	2.5 (10)
Total*	100.0 (391)	100.0 (398)

Data are % (n).

* Thirteen women had two types of microorganism with colony concentration of 100,000 colony-forming units per milliliter or more.

The causative pathogens for asymptomatic bacteriuria at recruitment in both groups were also similar. *Escherichia coli* was the most common causative bacteria at close to 50%, followed by *Staphylococcus saprophyticus*, *Enterococcus* spp, *Streptococcus* Group B, *Staphylococcus aureus*, *Enterobacter* spp, and *Klebsiella* spp (Table 2). However, when viewing the data, recall that Argentinean women with asymptomatic bacteriuria due to *Streptococcus* Group B were excluded from the trial, because their protocols required all such patients to receive a full 7-day course of antibiotics. After carefully reviewing the data, we realized that the causative bacteria in 23 recruited patients was *Staphylococcus* coagulase negative, which according to the protocol should not be considered as pathogens. Therefore these 23 patients were inappropriately recruited.

Bacteriologic cure rates evaluated at 14 days after treatment were 75.7% and 86.2% for 1-day and 7-day antibiotic treatment regimens, respectively. The cure rate difference was -10.5% (95% CI -16.1% to -4.9%) (Table 3 and Fig. 2) and the cure rate ratio was 0.88 (95% CI 0.82-0.94) (Table 3). Sensitivity analysis, in which all contaminated urine culture

results were assigned as either cure or not cure did not change the cure rate difference or cure rate ratio. Sensitivity analysis performed by excluding 23 inappropriately recruited patients did not change the cure rate difference or cure rate ratio. The 1-day regimen was thus statistically significantly less effective than the standard 7-day regimen. To follow the intention-to-treat principle, we did not exclude these 23 inappropriately recruited patients from the analysis.

During the 2 weeks that followed initiation of treatment, five women in the 1-day and six women in the 7-day group developed symptomatic UTI. The difference was not statistically significant. Similarly, from day 14 through delivery, there were 10 and 12 cases of symptomatic UTI in the 1-day and 7-day regimen groups, respectively. Again, the difference was not statistically significant. Overall, symptomatic UTIs were diagnosed in 15 (5+10) and 18 (6+12) women in the 1-day and 7-day regimen respectively, RR 0.86 (95% CI 0.44-1.67).

Incidences of preterm delivery (11.0% [39 of 353] compared with 8.9% [31 of 349]) and low birth weight (13.2% [48 of 364] compared with 8.0% [28 of 350]) were higher in the 1-day regimen group but the differences were not statistically significant. There was also no statistically significant difference in the risk of congenital malformations (1.4% [5 of 364] compared with 1.1% [4 of 350]) between the two groups. However, mean birth weight and mean gestational age at delivery were statistically significantly lower in the 1-day regimen group, 3,059 g compared with 3,159 g (mean difference -100, 95% CI -181 to -18) and 38.4 weeks compared with 38.7 weeks (mean difference -0.3, 95% CI -0.7 to -.005), respectively (Table 4). There was less nausea, headache, and other adverse effects but more flatulence in the 1-day regimen group, but the differences were not statistically significant (Table 5).

DISCUSSION

These data demonstrate that 1-day nitrofurantoin therapy is significantly less effective than the standard 7-day regimen in achieving bacteriologic cure when

Table 3. Bacteriologic Cure in Pregnant Women at 14 Days After the Initiation of Nitrofurantoin Treatment Between Two Regimens (Excluding Cases With Contamination Results) Adjusted by Centers

Regimen	Sample Women	Bacteriologic Cure [n (%)]	Cure Rate Difference (95% CI)	Cure Rate Ratio (95% CI)
1-day	371	281 (75.7)	-10.5 (-16.1 to -4.9)	0.88 (0.82-0.94)
7-day	370	319 (86.2)	0	1

CI, confidence interval.



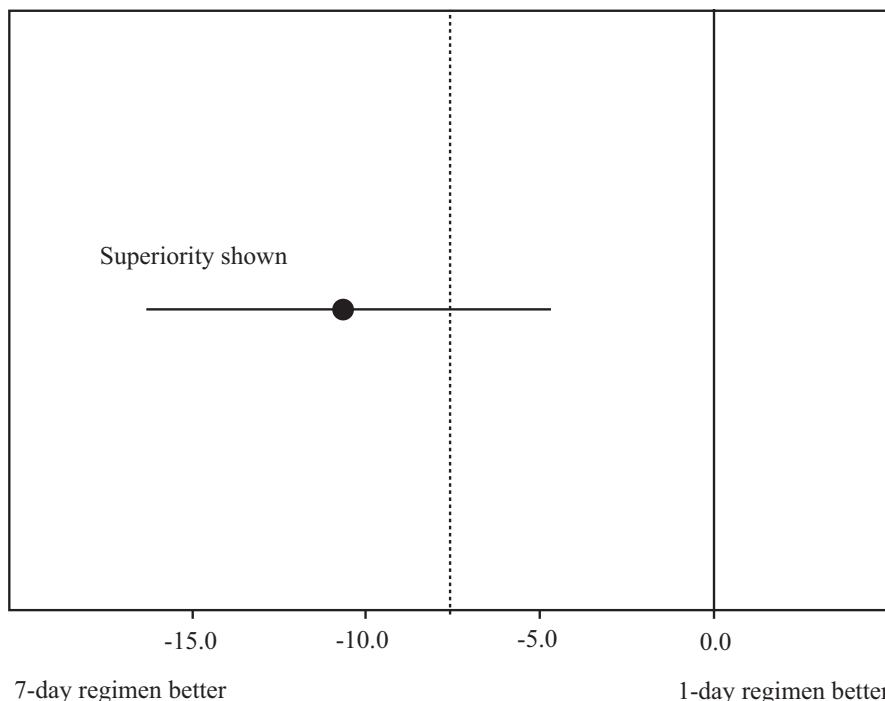


Fig. 2. Bacteriologic cure rate difference (%) with 1-day regimen compared with 7-day regimen. Vertical dotted line represents the margin of clinical equivalence determined a priori. Solid line represents the null effect.

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both approaches were evaluated 14 days after initiating treatment. Patients in the 1-day regimen group also had higher incidences of preterm delivery and low birth weight (not statistically significant), and lower mean birth weight and mean gestational age at delivery (statistically significant). However, the rates of symptomatic UTI were similar in both groups. Interestingly, the rate of clinical UTI was below 5%. Adverse effects were slightly lower in the 1-day regimen group (not statistically significant).

The strength of our findings are underscored by the study design, a multicenter double-blinded placebo-controlled randomized trial. Furthermore, all microbiologists were trained in dipslide technique, the laboratories and data regularly audited to assure high quality, and site visits were performed by WHO officials. There were also two investigators' meetings where trial problems were discussed and resolved. Loss to follow-up

after randomization and the number of contaminated specimens was minimal, the latter problem being also controlled with a sensitivity analysis, where the assumed best (all contaminated negative) or worst (all contaminated positive) did not change the result of primary outcome. All the factors summarized above combine to strengthen the validity of our conclusions.

We could not reach our target sample size of 992 women because we could not recruit 32% of the potential eligible subjects, as already described in the results section. However, we recruited 778 women, which represents 85% of our target sample size, permitting us demonstrate that 1-day nitrofurantoin regimen is significantly less effective than the standard 7-day regimen.

We update the Cochrane review⁷ by incorporating our data into the meta-analysis. Comparing "no cure rate" between 1-day and 4–7 day regimens using the random effects model, adding the data from our

Table 4. Pregnancy Outcomes by Regimen of Nitrofurantoin

Outcome	1-Day Regimen	7-Day Regimen	RR* (95% CI)/Mean Difference (95% CI)
Preterm delivery (GA less than 37 wk) (703 mothers)	39/354 (11.0)	31/349 (8.9)	1.24 (0.79–1.94)
Low birth weight (less than 2,500 g) (714 newborns)	48/364 (13.2)	28/350 (8.0)	1.55 (0.97–2.48)
Congenital malformations (714 newborns)	5/364 (1.4)	4/350 (1.1)	1.20 (0.33–4.44)
Birth weight, g (714 newborns)	3,059 ($\pm$ 582)	3,159 ($\pm$ 523)	–100 (–181 to –18)
Gestational age at delivery, y (703 mothers)	38.4 ($\pm$ 2.6)	38.7 ($\pm$ 2.0)	0.3 (–0.7 to –0.005)

RR, relative risk; CI, confidence interval; GA, gestational age.

Data are n/N (%) or mean ($\pm$ standard deviation) unless otherwise specified.

* Using 7-day regimen as a reference group.



Table 5. Adverse Effects During 14 Days After the Initiation of Treatment by Regimen of Nitrofurantoin

Adverse Effects	1-Day Regimen	7-Day Regimen	RR* (95% CI)
Nausea	23 (6.1)	33 (8.6)	0.72 (0.43–1.20)
Headache	17 (4.5)	22 (5.7)	0.79 (0.43–1.47)
Flatulence	15 (4.0)	9 (2.3)	1.71 (0.76–3.86)
Others	20 (5.3)	26 (6.8)	0.79 (0.45–1.39)
Total	375	385	

RR, relative risk; CI, confidence interval.

Data are n (%) unless otherwise specified.

* Using 7-day regimen as a reference group.

study changes the RR and 95% CI from 1.41 (0.80–2.50) to 1.42 (0.89–2.28). Although the confidence interval is narrower, we cannot conclude from the new meta-analysis that the 4–7 day regimen is significantly more effective than the 1-day regimen. There was significant heterogeneity in these meta-analyses, and unfortunately, only two included studies (Masterton et al¹⁶ 1985 and ours) had adequate allocation concealment, whereas all the other nine studies were classified as inadequate, unclear, or not used. We therefore calculated the pooled RR for these two trials with adequate methodology using a fixed effects model and found that the risk of no cure in the 1-day regimen is significantly higher than the 7-day regimen (RR 2.10, 95% CI 1.44–3.05).

In summary, our trial demonstrates that the 1-day regimen of nitrofurantoin is significantly less effective than the 7-day regimen. Adding these results to the other trial with adequate methodology (Masterton et al¹⁶ 1985 demonstrates that the 1-day regimen is significantly less effective than the 7-day regimen. We therefore conclude that women with asymptomatic bacteriuria in pregnancy should be treated by the standard 7-day regimen of nitrofurantoin, if such treatment is selected, until more data becomes available testing 7-day compared with 3- or 5-day regimens.

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Making stillbirths count, making numbers talk - Issues in data collection for stillbirths

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Abstract

Background: Stillbirths need to count. They constitute the majority of the world's perinatal deaths and yet, they are largely invisible. Simply counting stillbirths is only the first step in analysis and prevention. From a public health perspective, there is a need for information on timing and circumstances of death, associated conditions and underlying causes, and availability and quality of care. This information will guide efforts to prevent stillbirths and improve quality of care.

Discussion: In this report, we assess how different definitions and limits in registration affect data capture, and we discuss the specific challenges of stillbirth registration, with emphasis on implementation. We identify what data need to be captured, we suggest a dataset to cover core needs in registration and analysis of the different categories of stillbirths with causes and quality indicators, and we illustrate the experience in stillbirth registration from different cultural settings. Finally, we point out gaps that need attention in the International Classification of Diseases and review the qualities of alternative systems that have been tested in low- and middle-income settings.

Summary: Obtaining high-quality data will require consistent definitions for stillbirths, systematic population-based registration, better tools for surveys and verbal autopsies, capacity building and training in procedures to identify causes of death, locally adapted quality indicators, improved classification systems, and effective registration and reporting systems.

Background

Why count stillbirths?

The vast majority of stillbirths are preventable, and simple interventions could lead to healthy infants as a rich reward for the resources invested [1-6]. Mothers and families could be spared the emotional burden accompanying pregnancy loss, and societies could gain by reducing a major public health problem.

Being counted is essential. Stillbirths are estimated to account for more than half of the world's perinatal deaths, but only a fraction are registered in any health information system [7]. Stillbirths have been invisible in the World Health Organization (WHO) reports on the global burden of disease [8] and in the United Nations (UN) Millennium Development Goals and Targets. According to the most recent WHO reports on perinatal mortality, 90 countries worldwide lacked any kind of data on stillbirths [7,9]. Improvements in basic registrations of stillbirths are both possible and urgently needed [10]. The "Who Counts?" series in *The Lancet* argued forcefully for the need to build and strengthen civil registration and health information systems globally [11-14]. Systematic and reliable registration of stillbirths is crucial to any health care program planning in this field. Analysis and use of such data provide the fundamentals for accountability and funding. Prioritization of registration and analysis of neonatal deaths in the Millennium Development Goals led to a global effort resulting in significant gains in prevention [15]. Accurately counting stillbirths will similarly provide an opportunity to set specific goals, the first step toward any improvement.

Simply being counted, however, is insufficient for planning, monitoring, and continuously improving efforts to prevent stillbirths. Additional resources and political commitment are needed to improve basic health care services and to overcome limited governance, infrastructure, and workforce. Localities with limited resources are also vulnerable to low-quality health services, where lasting and sustained improvement will likely come through a redesign of health care systems, not through continued funding of current failing systems. In such situations, accessible data are needed on core indicators of quality and availability of care, as well as on the prevalence of underlying causes of these deaths and associated conditions which constitute the framework for understanding stillbirths (Figure 1).

The need for better data is a pressing issue in stillbirth prevention, where there is a significant gap in translating knowledge into proven strategies to reduce fetal mortality [16-20]. Better data on stillbirths are also needed for basic research, which has been neglected. For every 67 publications on unexplained infant death (SIDS) in PubMed, there is only one on the far more prevalent problem of unexplained stillbirths (using the search terms ("unexplained stillbirth*" [All Fields] OR "unexplained fetal death*" [All Fields]) vs. ("Sudden Infant Death" [MeSH] OR "sudden infant death*" [All Fields] OR "SIDS" [All Fields])). This research gap is especially pronounced in low-income countries in which the burden of stillbirths is particularly high. The general lack of data and of research to understand and prevent stillbirths in low-income countries adds to the "10/90 gap"--the fact that less than 10% of research resources address conditions affecting more than 90% of the world's population [21]. Of all publications on stillbirth in PubMed, only about 3% relate to low-income countries (using the search terms (("stillbirth" [MeSH Terms] OR stillbirth* OR "fetal death" [MeSH Terms] OR fetal death*) AND humans [MeSH Terms])) with or without (AND ("developing countries" [MeSH Terms] OR developing countr*)).

Addressing the issue of counting stillbirths is clearly complementary to traditional approaches to perinatal data collection that have prioritized neonatal and maternal deaths. In a continuum of perinatal deaths, data on stillbirths emphasize the earlier phases of pregnancy and bring information that may convey benefits for both maternal and child health. Antepartum and intrapartum stillbirths are strong and direct indicators of quality of prenatal and obstetric care. Also, stillbirth rates, highly correlated to maternal death rates, continue to be a sensitive indicator in less affected communities where maternal deaths are too few to serve as a sensitive indicator [22].

Although counting stillbirths seems simple, it is complex in practice. The incentives for an individual to be counted in civil registration systems are linked to the perceived benefits [11]. For stillbirths, such incentives may not be obvious in communities where few advances in health care are offered. Apparent cultural resistance to registration can be considerable, making data collection problematic if context and culture are not sensitively addressed. In low-income countries, the conduct of even the most well-designed, population-based studies on still-

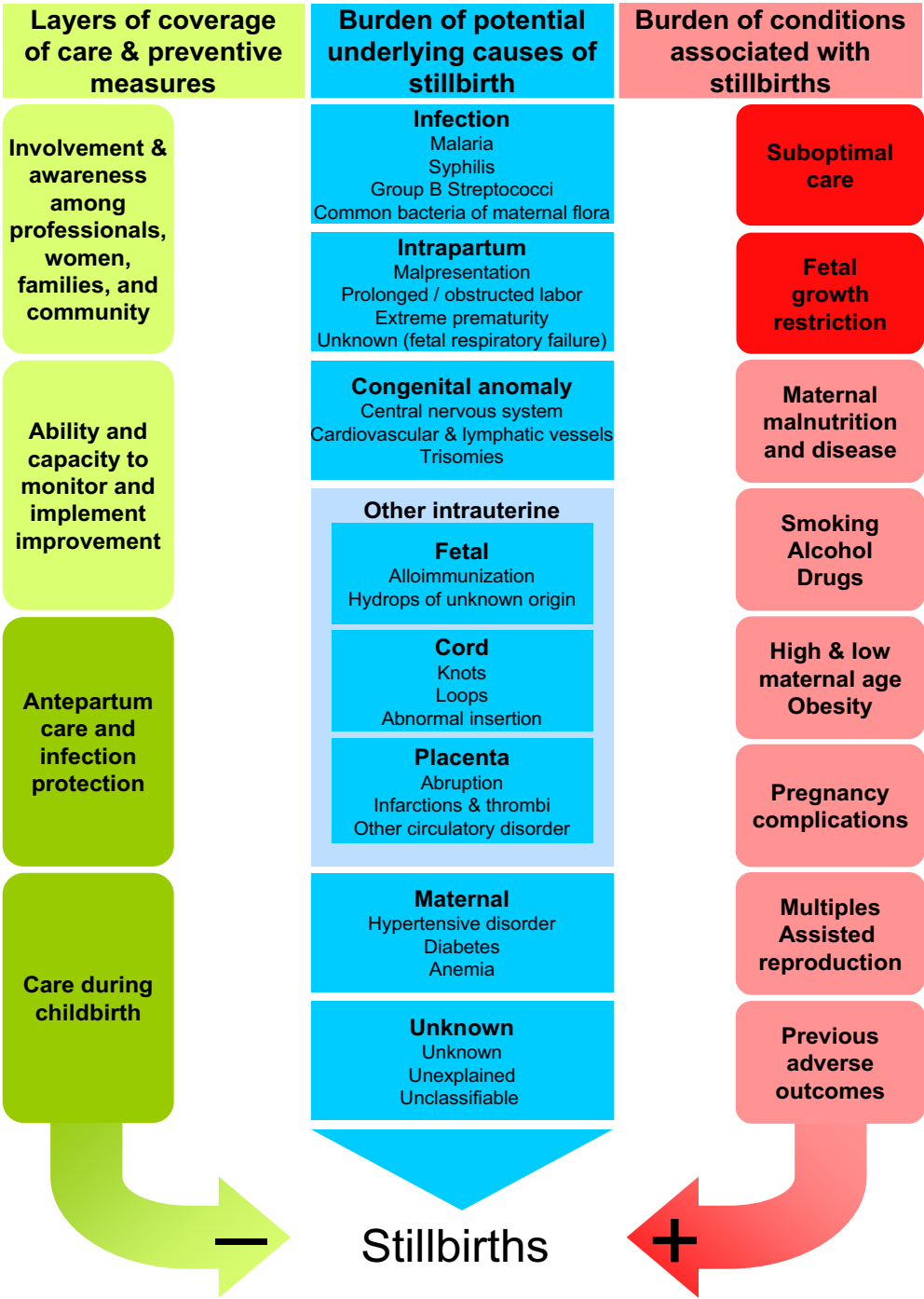


Figure 1
Stillbirth determinants. A framework of the setting and conditions that constitute the data sources needed for the understanding of stillbirth mortality. The classification of significant proportions of underlying causes of death globally is reproduced from CODAC simplified [50].

births weighing more than 1000 g, has been met with difficulties as many stillborn infants are never weighed [10,18].

In this report, we assess how different definitions and limits in registration affect data capture, and we discuss the specific challenges of stillbirth registration, with emphasis on implementation. We identify what data need to be captured, we suggest a dataset to cover core needs in registration and analysis of the different categories of stillbirths with causes and quality indicators, and we illustrate the experience in stillbirth registration from different cultural settings. Finally, we point out gaps that need attention in the International Classification of Diseases (ICD) and review the qualities of alternative systems that have been tested in low- and middle-income settings.

Discussion

International definition and effects on data capture

The WHO/ICD defines stillbirths as the death of a fetus that has reached a birth weight of 500 g, or if birth weight is unavailable, gestational age of 22 weeks or crown-to-heel length of 25 cm (Figure 2) [23]. The WHO also recommends using a higher limit (1000 g/28 weeks/35 cm)

of third-trimester stillbirths for international comparisons [23]. Failure to adhere to WHO definitions and recommendations hampers stillbirth epidemiology. In the USA alone, reporting requirements are determined by individual states, and nine different definitions are used [24]; similar inconsistencies exist in Europe [25]. Reports that include higher rates of early stillbirths typically demonstrate higher rates of congenital anomalies, infections, and placental abruptions, which would suggest a need for different health care planning than in locations that report only third-trimester stillbirths [26-28].

Birth weight, thought to be more reliably reported, takes priority over gestational age in the WHO definition. Most high-resource countries have legislation related to stillbirth registration and reporting, with limitations almost uniformly based on gestational age ranging from 16 to 28 weeks [24,25,29]. In low-resource countries with scarce access to prenatal care and ultrasound dating of pregnancy, the accurate gestational age is seldom known. Differences in technical and cultural understanding of pregnancy duration adds to the problem, as both women and their care providers may count the number and variants of months (calendar, lunar or menstrual cycles) in

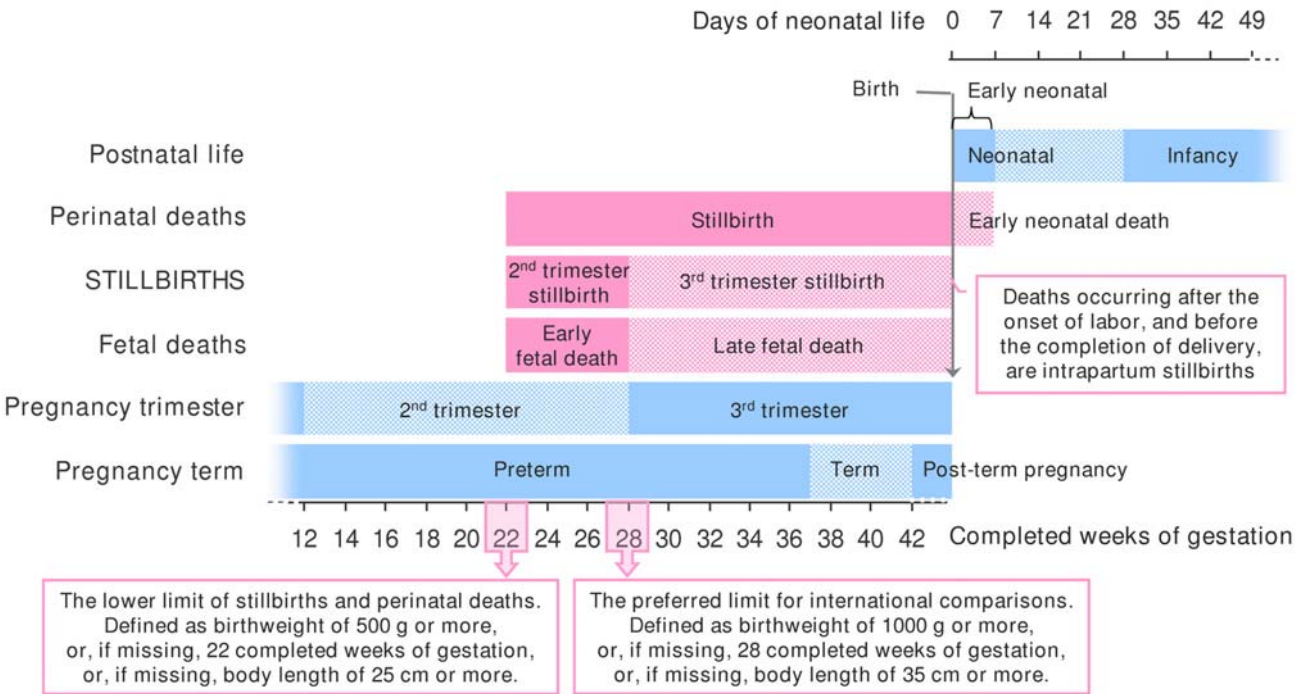


Figure 2
Definition of stillbirth. The definitions of stillbirth used by WHO and ICD in the framework of the continuum of perinatal losses and commonly used definitions of timing of pregnancy and newborn life. Categories of deaths in pink and periods of perinatal life in blue.

various ways [30,31], traditional pregnancy calendars may not add up to 280 days (e.g. the traditional Chinese lunar calendar of ten pregnancy months represents 293 days), and an early spontaneous abortion may not be perceived as the end of a pregnancy but that gestation may be included in the duration of the subsequent pregnancy [32].

Capture by birth weight yields lower stillbirth rates than capture by gestational age (Figure 3); therefore, a high-income country registering stillbirths after 22 weeks and subsequently reporting their numbers according to the 500-g birth weight limit will potentially underreport significantly. If these capture methods are applied to the Norwegian 1997-2007 data (compared with capture by either gestation or weight individually), 4.4% of stillbirths of ≥ 500 g occurring before 22 completed weeks of gestation are lost by the registration limits, and 18.6% of deaths after 22 completed weeks that weigh <500 g at birth are lost by reporting limits. In Australia, while reporting practices may also influence variations seen in reported stillbirth rates, nationally reported rates for 2006 from one agency (Australian Bureau of Statistics, <http://www.ausstats.abs.gov.au>) where birth weight (400 g) takes precedence over gestational age (20 weeks) are 30% lower than those from the other national agency (National Perinatal Statistics Unit, <http://www.npsu.unsw.edu.au>) where birth weight and/or gestation is used (5.2 v 7.4/1000, respectively). The true difference in stillbirth rates between high vs. low income countries is therefore larger than official statistics indicate. This gap will likely be greater in areas with higher rates of intrauterine fetal growth restriction, i.e., in low-resource regions. Underreporting will be an issue when registration

limits are the same as the intended reporting limits. Hence, registrations should aim to document fetal mortality occurring earlier than the limits at which they aim to report for comparative purposes, e.g., 20 weeks/400 g and 26 weeks/750 g, to report accurately at 500 g and 1000 g, respectively [33].

Identification of stillbirths

Beyond the heightened awareness of stillbirths needed to plan vital records or Demographic and Health Surveys to accommodate stillbirth registration in the many countries that lack any data on stillbirths, there are special issues that need to be addressed, providing both challenges and opportunities. An initial challenge is the ability of birth attendants in low-resource areas to identify an infant as stillborn. While the definition of fetal death requires that no heartbeat be present, there is often no ascertainment of such vital signs in settings where no resuscitation is attempted in the live-born but apparently lifeless newborn; such a newborn will be classified as stillborn if he or she does not recover spontaneously [34]. Higher coverage of the diagnostic tools and skills of neonatal resuscitation will improve correct registrations and, more importantly, prevent such apparent stillbirths [34,35].

Registration can only be successful if perceived as beneficial by the population being registered and by those responsible for collecting and reporting events. For the mother and her family, there may be no apparent benefits in terms of civil rights, health care, or other societal advantages normally awarded to mother and infant. In some settings, there are economic disadvantages for parents when a stillbirth is registered (Appendix 4). There is a lack of literature which directly assesses the factors that affect disclosure of stillbirths. However, areas that need attention to enable culturally sensitive data collection may be gleaned from practices in disclosure of pregnancy, the perception of stillbirth and the stillborn, and the context in which women make their health care choices.

In some cultures a new pregnancy is a celebrated event disclosed early in gestation, but a recurrent issue emanating from many low-resource settings is the risk associated with disclosure of pregnancy, which may outweigh perceived benefits. Not only is pregnancy in itself frequently seen as a state of shame and impurity [36], but the pregnant woman may see herself as a prime target for spirit-induced illness, witchcraft and other supernatural forces [37,38]. Such threats to herself and her baby may be perceived as a larger risk than biomedical causes [37], and since seeking health care may increase public exposure and risk, while biomedicine may not help against spirits [37-40], silence and hiding may be the first expressions of prenatal caring in their setting [37]. In the case of a pregnancy loss, disclosure may put both the woman's social

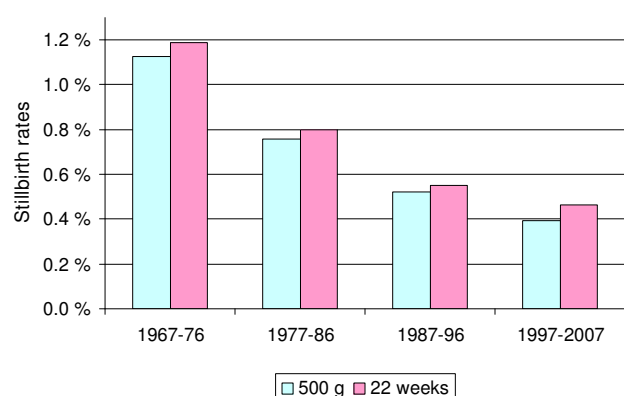


Figure 3
Stillbirth rates by reporting criteria. Norwegian stillbirth rates according to reports based on weight or gestational age. The data include 2.4 million births and 13,100 stillbirths in the Medical Birth Registry of the Norwegian Institute of Public Health.

status and future pregnancies at risk through community judgement of perceived "sins" which may include unfaithfulness, bewitching of her husband, possession by spirits or being a spirit wife of another man, illegal abortion or reproductive incapacity. Such community judgement may result in the women being abandoned or having to pay back the bride price [36,37,41]. Stillbirth is painful in all cultures, and the more problematic emotions are involved, and the less social support and acknowledgement of their loss received, the more complicated their grief [42-44]. Some parents affected by stillbirth receive massive support and recognition of their loss, but in different settings a woman's stillborn child may not be perceived as a significant "entity" and public displays of mourning may be culturally prohibited [36] - making any conversation about her stillbirth difficult. The need to assess the local perceptions of factors facilitating or obstructing stillbirth disclosure, and its ramifications, in planning the methods for data collection in a sensitive, private and confidential manner cannot be overestimated.

For the birth attendant, with first-hand knowledge of the event, there may be barriers to reporting as well. In most communities and for many reasons, health care professionals traditionally tend to underreport adverse events and outcomes, irrespective of whether they are objectively to blame for the event [45,46]. A blame culture with its inherent threat of punishment may result in the health professional's refuse to offer care to pregnancies with known complications, and reluctance to report adverse outcomes [40]. Despite a changing culture from individual blame to a system-approach to adverse events in many health care organizations [47], the health care professional attending births must still be expected to underreport intrapartum deaths unless provided with strong incentives. In communities where most births take place in institutions which provide maternity care, such barriers can potentially be overcome more easily, while they remain a major problem for stillbirths among women in rural areas who give birth at home. The objective lack of health care resources, accessibility and infrastructure, together with subjective maternal views of inadequate quality of care and lack of sensitivity to privacy and social, religious and cultural needs, will continue to prevent a large proportion of births from occurring in institutions in the foreseeable future.

Some of the challenges of capturing data on stillbirths in areas with high birth rates outside birthing institutions may be addressed by ensuring the registration of pregnancies before the perinatal period, if coupled with incentives such as access to antenatal care, allocation to maternity groups, dietary supplements, or other benefits - sufficient to outweigh the perceived risks of disclosing their pregnancy. This strategy will provide the most accurate

denominator, unbiased by maternal or professional barriers, and also provide important opportunities for initial risk assessment and essential preventive measures. With sufficient incentives to register a live-born baby, special focus to document outcomes should be planned for those registered as pregnant but not presenting for birth registration. By registering the mother rather than the infant, pregnancy outcomes lost to follow-up may be captured at subsequent pregnancy registrations, as women experiencing loss have higher rates of renewed pregnancy than those having a live-born child. If health professionals clearly communicate that disclosure of previous stillbirths may aid in preventing recurrence, mothers may also find personal motivation to overcome obstacles in reporting their stillbirth.

Causes and conditions to be captured

Considerable differences in causes and timing of stillbirths exist between populations, and these vary with the stillbirth rates. The setting and epidemiology of causes of death will define the most critical information on stillbirths needed to inform prevention and guide selection of the analyses that will provide the best indicators of improvement.

Longitudinal data from high-resource countries show that the rate of intrapartum stillbirths has fallen with improvements in intrapartum care [48]. Intrapartum death rates are therefore frequently used as an indicator of quality of care. As the rate of intrapartum stillbirths is directly associated with the availability of intrapartum care, a larger proportion of stillbirths occur in the intrapartum period in low- and middle-income than in high-income countries (31% vs. 16% of stillbirths, respectively) [48]. In Western Africa, the intrapartum stillbirth rate was estimated at 15/1000 in 2004 (36% of stillbirths), 50 times higher than the rate in North America of 0.3/1000 (10% of stillbirths) [7,49].

Preventability of intrapartum deaths will depend largely on gestational age, and timing of deaths should be registered both in terms of early versus late gestational deaths and, if known, whether the death occurred antepartum or intrapartum. Neither "intrapartum" nor "intrapartum asphyxia" are underlying causes of death but rather timing and final mechanism, respectively [50]. Such categories alone contain insufficient information to guide targeted improvements in care. When the most basic care is available, a majority of intrapartum deaths are caused by placental, cord, infectious, traumatic, and other specific complications, both in high- and low-resource countries [51-54]. Reports from Pakistan, Palestine, and South Africa all indicate that about one third of cases are linked to suboptimal care [53,55,56]. Characteristics and predisposing risks, such as plurality and maternal size, should

be registered together with events and conditions presenting during the intrapartum period, as should information on the level and quality of care available and received, as indicated in the dataset template.

Irrespective of setting, the largest proportion of stillbirths are antepartum deaths. Although availability of a timely delivery is critically important to prevention, the pregnancy at risk for antepartum death, and the optimal timing of delivery to prevent it, must first be identified through antenatal care. Adverse pregnancy outcome can be most effectively anticipated, prevented, and treated through implementation of adequate antenatal care. Components of this care include counselling and initiation of health-promoting efforts, such as proper nutrition or insecticide-treated mosquito nets, combined with screening, identification, and monitoring of pregnancy risks [3-6].

The reported prevalence of major causes of antepartum deaths will differ between high- and low-resource communities, because of both their true prevalence and the coverage of adequate evaluation to identify and register the cause of death [41]. Adverse antepartum conditions are often complex and can be found in the mother, the fetus, the placenta, and the umbilical cord, and their interactions. On a global scale, syphilis, malaria, and other infections; congenital anomalies; placental abruptions and other placental insufficiencies; and pregnancy-induced hypertension cause most antepartum deaths [2,16,17,20,54,57-63]. Placental pathology, including those cases manifesting clinically as maternal hypertensive disorders, contribute to the underlying cause of death in 6 out of 10 stillbirths in low-income countries [49,64]. In low-resource settings, this condition may more often go untreated and progress to severe preeclampsia or eclampsia and be classified as such. Because of infrequent examinations of the placenta, such cases are likely to be classified as deaths of unknown cause associated with fetal growth restriction or maternal hypertensive disease rather than by the underlying placental cause. While an appreciation of the maternal and fetal conditions associated with placental pathology is important in risk reduction in both high- and low-resource country settings, lack of information about placental pathology still inhibits better understanding of etiology of these deaths.

The relative contribution of congenital anomalies to stillbirth rates in low-resource countries is low because of the high rates of other causes coupled with an under-diagnosis of malformations due to relying on findings from gross external malformations when autopsy and other diagnostic assessments are lacking. In countries with liberal abortion laws, however, the contribution of anomalies is often underestimated as a result of antenatal diagnoses and ter-

minations of pregnancy before the perinatal period. In evaluating mortality rates associated with anomalies in communities with high coverage of prenatal ultrasound and access to medical termination of pregnancy, termination rates must therefore be taken into account [65].

The largest contributors to third-trimester stillbirths of infectious causes in the low-income world are malaria and syphilis [2,63], while typical pathogens in high-income countries are probably mostly missed in low-resource settings because of the specialized tests needed to identify them adequately, as in the case of group-B streptococci, Parvovirus B-19, *Listeria monocytogenes*, and early-gestation infections by common bacteria of maternal intestinal flora. Such undetected infections will also add to the group of antepartum stillbirths of unknown cause. Unknown cause of death may mean two different things in high- and low-income countries. There is a wide gap between unexplained stillbirths despite adequate post-mortem examinations, which represent one fourth of antepartum stillbirths in high-resource settings [66,67], and stillbirths of unknown cause resulting from a lack of information or examinations, which represent up to two thirds of antepartum deaths in communities where either suboptimal testing is performed or causes of death are poorly classified, both in high and low-income settings [68-70]. Addressing the challenges in evaluation of stillbirths of unknown cause, and prevention of unexplained stillbirths, requires that such entities are registered among causes, as discussed later.

Despite such differences, which make direct comparisons across populations difficult, low-resource communities should aspire to register their stillbirths in the same systematic manner as in settings with greater resources. A common classification system is needed to build a common understanding and bridge the knowledge gap. At the same time, it is essential for low-income countries to also collect basic data such as information on timing of death and fetal growth restriction in these same datasets.

Datasets of stillbirths

Data on stillbirths should enable the analysis and monitoring of quality of care and the most prominent specific threats to reproductive health. Relying on "general improvement" of health and health care in the population will be insufficient. Reducing stillbirth rates in Scandinavia from levels currently seen in low-income countries to those seen today has taken more than 100 years [71]. Cause-specific interventions have been shown to be effective in reducing stillbirth rates [1,2,19,72]. The template dataset presented here (Figure 4) has been designed specifically to identify and monitor significant threats to pregnancy health that health care programs can address, both within quality of care and among the most prevalent

causes of death and associated conditions globally. Examples of challenges and opportunities for such data collections are presented in Appendices 1, 2, 3 and 4.

In this template, the main underlying cause of death should be registered, and up to two associated conditions may be added to capture data on the scenario in cases with complex or multiple causes. It includes case details needed to analyze the potential for prevention and to correct for case mix when comparing populations. It also includes some of the basic measures of quality and availability of care, although more detailed information needs to be gathered to monitor specific interventions. In particular, measures of quality of care need to reflect local challenges to be helpful for further improvement [73-75]. National or local guidelines should define what is considered as adequate care versus suboptimal care, depending on which evidence-based interventions that can be provided [3-6], and this dataset segregates deficiencies according to whether suboptimal care was the result of lacking coverage (adequate care not available) or insufficient health care delivery and usage.

Most of the suggested data items are easily observed by a skilled birth attendant in most settings and will be sufficient for classification in main categories of causes of death, as illustrated in Figure 1. A large proportion of stillbirths do, however, occur in settings where the mother has received no antenatal care and gives birth at home with no skilled attendant present. In this situation, a verbal autopsy, taken after the birth, offers a potential source of helpful data. The abolition of pregnant women lacking any maternity health care is already targeted as the primary goal in any preventive strategy against maternal and perinatal deaths. Implementation of basic maternity health care to improve pregnancy outcome is not dependent on knowledge of specific causes of stillbirth within the setting within which it is delivered. Current knowledge is sufficient for remedial action, and the will and ability to change are the only things lacking to mobilize a call to action. Substandard situations must not scale down ambitions for better data collection; rather, the ability to identify causes of death should be scaled up. The template dataset provides the opportunity to register data items as unknown, and the frequency of unknown data should be monitored as a quality indicator together with the rate of stillbirths classified as cause unknown.

The current system for verbal autopsy does seem to provide useful information on the causes of death in most cases, but it still has unsolved issues for stillbirths [76,77]. With the most prevalent causes of death in stillbirths in mind, efforts to improve the value of verbal autopsy should be a priority. Ideally, some level of skilled post-mortem investigation, at least an external macroscopic

examination, should be performed [78]. Birth attendants can be trained to use illustrations on posters to assess the degree of maceration and determine approximately when fetal death occurred, but international standards for verbal autopsy for unattended home deliveries resulting in stillbirth are lacking [79]. Tools to determine pathologies of the placenta for birth attendants in low-resource areas should be developed and tested. The tools would help birth attendants collect basic, but important, information such as placental-fetal birth weight ratio, gross description of placental dimensions and shape and umbilical cord insertion, color and smell indicating infections, detection of clots and sign of abruption, large infarcts, and widespread fibrosis. In settings where autopsies are never performed, protocols that include placental examination often provide valuable data for capturing the cause of death [61,80]. Regrettably, examination of the placenta is often omitted because of lacking resources, training, and protection against contaminated blood, and poor understanding of its clinical importance in identifying the cause of death. Cultural practices may also prevent such examinations, as e.g. in China, Pacific Islands and West Africa, where the placenta may be of high symbolic and spiritual importance, and should be eaten or buried at specific sites.

Although this report focuses on the specific needs to capture data on stillbirths, neonatal conditions and deaths should be included in the same system to ensure a full picture of perinatal mortality, linked to maternal conditions and causes of death. In particular, causes and mechanisms of neonatal deaths within 12-24 hours of life are generally the same as for intrapartum stillbirths [81].

Classification of causes of death and associated conditions

Classification systems for stillbirths may be useful if designed for comparison of communities, for audit of care, and for planning and monitoring prevention and research. Besides the ICD system, there is no international consensus on a classification system for stillbirths. The ICD aims to classify the underlying cause of death, and when not available, the condition most likely to have resulted in death. It is used extensively in low-income countries, for example, to report perinatal mortality to WHO. The ICD system was developed to allow the systematic coding, analysis, interpretation, and comparison of mortality and morbidity, but it is not adapted specifically to stillbirth. Thus, the current ICD-10 does not fully recognize the stillborn infant (with cord, placenta, and membranes) as an individual entity with its own diseases, conditions, and events to be registered separately from the mother. There are limited codes for conditions specific to the perinatal period in the O codes ("pregnancy, childbirth, and puerperium," from the maternal perspective) and P codes ("certain conditions originating in the perina-

Figure 4
Dataset template for stillbirths. A template for the development of data collection forms for datasets of stillbirths.

tal period," from the fetal perspective), where adequate coding for stillbirths should be found. The placental codes in particular are incomplete and can only be used for a few of the placental pathologies affecting pregnancy outcomes. This lack of coding options is further complicated by our incomplete understanding and continued controversy regarding various placental findings and their causality in stillbirths. There is also considerable overlap between O and P codes that may result in confusion for allocation. WHO advocates the accurate use of ICD codes to monitor the quality of registrations of causes of death, but the range of incomplete categories of stillbirths in ICD-10 suggest that for now, other indicators of quality must be defined. The current revision of the ICD system (ICD-11) is expected to be released in 2013.

With these limitations in the ICD system, and with the many different purposes of classification, a number of alternative and mostly mutually incompatible classifications for stillbirths have been designed over the past decades [82]. A classification system should be an information management tool [49,50]. Depending on the purpose (local health care monitoring, planning, or research), different classification systems may be helpful, and a perfect all-purpose system is unthinkable. Although classifications are typically used in low-income countries to identify the main areas of preventive efforts [83,84], none of them has been rigorously tested to determine the effects on stillbirth prevention and rates after implementation. A core classification system for the main categories of causes of death and associated risk factors and conditions in stillbirths, as collected in our proposed dataset template, is nonetheless the starting point. For international comparisons to be meaningful, the most prevalent low-income country-related causes and conditions must be included in the classifications. Most current classifications have been created for high-income countries and implemented in low- and middle-income countries without modifications. Typically, a system for a high-resource setting will not be poised to adequately manage information on, for example, intrapartum deaths or infections such as malaria and syphilis. A base system needs some fundamental elements, and the corresponding characteristics of the few that have been tested in low- and middle-income countries are listed in Table 1.

1) Compatibility with ICD. The aim should be to supplement the ICD system, and to ensure compatibility, a tracking system for stillbirths should adhere to the concepts of capturing the underlying causes. Although additional information, such as the specific identification of potentially preventable associated conditions, may be beneficial, its inclusion should not make the system incompatible with ICD concepts.

2) Expandability of classifications. To be perceived as useful in all settings, the basic categories should allow the simplicity of data collection from verbal autopsies. Yet, these categories should also be expandable to the individual diagnoses registered in high-resource, high-expertise settings to promote consistency across populations and facilitate knowledge transfer. The Causes of Death and Associated Conditions (CODAC) classification is used as one such example for illustration in Figure 5, where the first case could be identified by verbal autopsy as an intrauterine infection with foul-smelling amniotic fluid and maternal fever, and diagnosed in other settings as an ascending *E. coli* infection confirmed by cultures from internal fetal tissues. Second, an obvious congenital anomaly of the head could be subclassified as hydranencephaly in a specialized center for perinatal pathology. Third, a case identified in low-resource settings as a small baby with a rubber-hard placenta with white-gray lesions, can be identified by perinatal pathologists as massive perivillous fibrin depositions. Using expandable classifications, data collection is possible for all, yet none are restricted by a too-simplistic system from preserving more complex information.

3) Capture of intrapartum events. A data system should include categories to distinguish items on antepartum and intrapartum conditions that are targets of preventive efforts in antenatal and intrapartum care, as in the dataset we present here. Specifically, it should not only state that death occurred in the intrapartum period, but also capture the actual intrapartum events. As an example, the Wigglesworth system mainly focuses on timing of death, which is favoured in many low-resource settings because its simplicity allows any birth attendants to use it irrespective of his or her educational level. Yet, in its original version, it did not handle any information other than timing and congenital malformations, and the simplicity of the system does not outweigh the loss of information [84,85]. A classification system without information on intrapartum events will be of little use in one third of stillbirths globally.

4) Capture of placental conditions. The conditions affecting the stillborn infant that are related to the adjoining cord, placenta, and membranes need to be recorded. Of particular importance is managing the information on the placenta, as this is lacking in the current ICD.

5) Ability to differentiate unknown and unexplained events. While infections like syphilis provide direct causes of death as targets for prevention and should be included, the category of "unknown" events in antepartum and intrapartum deaths also provides

Table 1: Classification systems and their characteristics for use in low- and middle-income countries

Systems tested in low- or middle-income countries	Number of categories of stillbirths ^a	Are intrapartum events captured in subcategories?	Does the system aim to capture underlying cause?	Are the main categories consistent with underlying cause?	Resources desirable for use ^b	Does the system separate unknown from unexplained?	Agreement tested (Kappa score or level of agreement)	References
Aberdeen	8-0-0	no	yes	no	B	no	0.35-0.97	[49,84,93-95]
CODAC	10-94-577	yes	yes	yes	B, C	yes	0.65-0.94	[49,50]
CODAC Simplified	10-30	yes	yes	yes	B, C	yes	no	[50]
ICD-10	17-134	yes	yes	yes/no	B	no	no	[23]
Nordic Baltic	13-0-0	no	no	no	A	no	0.85	[84]
Patinson ^c	12-48-0	yes	no	no	B	no	no	[96,97]
PSANZ-PDC	11-52-33	yes/no	yes	yes/no	B, C	yes	0.63-0.90	[49,86]
ReCoDe	9-28-1	yes/no	no	no	B, C	yes	0.51	[49,98]
Tulip	6-24-7	no/yes	yes	yes	B, C	yes	0.74-0.86	[49,87]
Whitfield ^c	12-15-2	no	yes	no	B	no	no	[95,99]
Wigglesworth	5-0-0	no	no	no	A	no	0.25-0.85	[49,84]

^aNumber of main categories followed by subcategories.

^bA = little investigations and no placental examinations necessary; B = some clinical and pathological investigations necessary or desirable; C = placental investigations necessary or desirable (placental conditions included in the classification).

^cModified versions of the Aberdeen classification.

Acronyms: CODAC: Causes of Death and Associated Conditions, PSANZ-PDC: Perinatal Society of Australia and New Zealand Perinatal Death Classification, ReCoDe: Relevant Conditions of Death.

Verbal autopsy	Level I	Level II	Level III
Infection	0 Infection	00 Unspecified or other 02 Malaria 04 Syphilis 05 GBS 06 Common bacteria of maternal flora	• 060 Unspecified • 061 Enterobacter species • 062 Enterococci species • 063 Escherichia coli • 064 Klebsiella species • 065 Mycoplasma species • 066 Staphylococci species • 067 Streptococci species (non-B) • 068 Ureaplasma urealyticum • 069 Other
Intrapartum	2 Intrapartum	20 Unspecified or other 23 Malpresentation 25 Prolonged / obstructed labor 26 Extreme prematurity 29 Unknown (fetal resp. failure)	
Congenital anomaly	3 Congenital anomaly	30 Unspecified or other 31 Central nervous system 32 Cardiovasc. & lymphatic vessels 37 Trisomies	• 310 Unspecified • 311 Anencephaly • 312 Craniorachischisis • 313 Holoprosencephaly • 314 Hydranencephaly • 315 Hydrocephalus • 316 Microcephaly • 319 Other
Other intrauterine	4 Fetal	40 Unspecified or other 43 Alloimmunization 47 Hydrops of unknown origin	
	5 Cord	50 Unspecified or other 51 Knots 52 Loops 53 Abnormal insertion	
	6 Placenta	60 Unspecified or other 63 Abruptio 64 Infarctions & thrombi 65 Other circulatory disorder	• 650 Unspecified • 651 Fetal thrombotic vasculopathy and stem vessel thrombi • 652 Fetal vascular narrowing • 653 Hemorrhagic endovasculitis • 654 Subchorionic fibrin deposition • 655 Perivillous fibrin deposition • 656 Intravillous fibrin deposition • 657 Massive basal plate fibrin dep. ("Maternal floor infarct") • 658 Massive parenchymal fibrin deposition ("Glitterinfarct") • 659 Other
Maternal	7 Maternal	70 Unspecified or other 71 Hypertensive disorder 73 Diabetes 75 Anemia	
Unknown	8 Unknown	80 Unspecified or other 81 Unknown 86 Unexplained 87 Unclassifiable	

Figure 5

Causes of death in stillbirth. Expandable layers of causes of death according to the resources available for evaluations of stillbirths. Select categories of the CODAC classification system [50] used for illustration.

indirect operational causes with opportunity for improvement that should be targeted, as shown in Figure 6. The classification system should enable differentiation between unknown and unexplained causes of death to allow meaningful analysis that takes into account the proportion of items that are unknown in the dataset. Ideally, one would expect unexplained stillbirths to be stillbirths "(...) unexpected by history and in which a thorough autopsy (...), together with gross and histological examination of the umbilical cord, placenta, and membranes, fails to demonstrate an adequate cause of death." [67].

Of the existing classification systems that have been tested in low- or middle-income country settings, only the current versions of the Perinatal Society of Australia and New Zealand Perinatal Death Classification (PSANZ-PDC) [86] and Causes of Death and Associated Conditions CODAC [50] comply with all five of these requirements, although the basic level of the main categories may have to be simplified further to be used with verbal autopsy data only. The summary in the Table 1 would indicate that Tulip [87] requires only the addition of an explicit category for intrapartum events to comply (intrapartum causes are embedded in other categories in Tulip). Tulip is uniquely organized to capture information from a high-

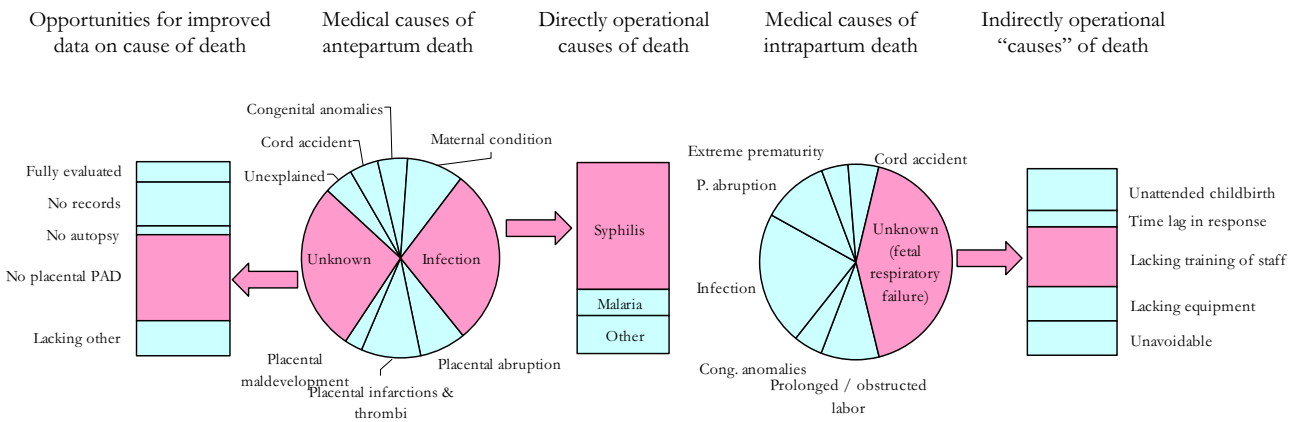


Figure 6
Operational causes of death. Examples of causes of antepartum and intrapartum deaths that may be targeted directly for stillbirth prevention (e.g., syphilis) or indirectly to improve clinical quality of care or ability to capture data for further improvement. PAD: pathological-anatomical diagnosis.

resource, high-expertise setting with focus on the detailed diagnosis of malformations and placental abnormalities [64,87], and it is not intended for use in low- and middle-income country settings.

The two systems that seem to be the best options to supplement ICD, CODAC and PSANZ-PDC, are among the systems in which some clinical, pathological, and placental investigations would be necessary or desirable to ensure consistency in coding (Table 1). This follows from the inclusion of the placenta as an entity to capture. To set lower standards and accept a lack of data on conditions contributing to two thirds of antepartum stillbirths in high-income countries [19,49,64] is not a viable alternative. Use of the more elaborate systems may introduce misclassification in a setting with low resources. For instance, placental and infectious causes may be underdiagnosed, classified instead as unknown causes. However, although the value of placental histopathology and autopsy is undisputed in high-resource countries [88-90], the potential for prevention (for society and for the mother's subsequent pregnancies) associated with elaborate post-mortem testing in low-income countries is unclear, and the minimum level of investigation needed to classify a cause of death as unexplained rather than unknown in low- and middle-income country settings must be defined. For the purpose of data collection from verbal autopsies, categories such as "fetal," "cord," and "placenta," typically found in many classifications, could easily be combined, e.g., into "other intrauterine," as exemplified in Figure 5. The underlying cause of fetal hydrops or location of an intrauterine infection as either

fetal, cord, or placenta will be particularly difficult to decide.

The number of categories per system reflects the amount of information captured by that system (Table 1), but it does not necessarily reflect the applicability of these categories for analyzing stillbirth scenarios in all settings. The ease of use with little information versus more information requiring more resources for investigations must be balanced by the local knowledge of its intended use. Interestingly, testing the ease of use and ability to capture pertinent information on stillbirths in both high- and low-resource settings demonstrated that the complexity of the three systems mentioned previously was not associated with reduced user-friendliness. On the contrary, health professionals coding stillbirths seem to prefer having the opportunity to code exact information rather than registering information in broader and more vague categories [49,50], and all complex systems also have broader categories for comparisons that are detailed in subcategories.

It is time that traditional classifications such as Wigglesworth be celebrated for past achievements and substituted with classification systems that manage the information currently available. Several dozen classification systems exist already. However, some of these systems still require testing, and new systems must be developed specifically to handle verbal autopsy data. Such improvements in data management are essential to informing targeted interventions to prevent stillbirths. As the ultimate goal is stillbirth prevention, future research in the development and use of classification systems should aim to document its usefulness in this respect.

Summary

Scaled-up of coverage of registration of births is needed. Vital registrations and health information systems and other large Demographic and Health Surveys should be adjusted to accommodate registration of stillbirths. Tools for verbal autopsies must be revised to improve capture of causes and events related to stillbirths. The WHO definitions of stillbirth for reporting should be implemented globally, and registrations should capture stillbirths of lower weight and gestation than the intended reporting limits. Pregnancies should be registered before the perinatal period to help overcome the barriers in stillbirth registration and enable prevention efforts in antenatal care. Causes of death in stillbirths must be monitored, and better detection of the most prevalent causes--in particular, infections and placental pathologies--is needed. The ICD system's O and P codes need to be adjusted and supplemented to capture the causes identified. A universal approach to stillbirth classification is optimal and warrants focused attention.

The *BMC Pregnancy and Childbirth* issue on stillbirth prevention illustrates how specific causes of stillbirth can be prevented [3-5,5,6,41,91,92]. None of this will happen without data. Development and evaluation of prevention efforts require registration of all stillbirths, the characteristics of the pregnancies affected, the timing of death, the underlying causes, and the quality and availability of care for each individual. Stillbirths need to count. With careful collection and analysis of these data, the numbers will speak for themselves.

Abbreviations

WHO: World Health Organization; ICD: International Classification of Diseases.

Competing interests

The authors declare that they have no competing interests.

Appendices

Appendix 1 - Success criteria for collection and reporting of stillbirth data

- Consistent use of definitions between institutions
- Systematic approach to capture pregnancies and out-of-hospital stillbirths
- Capacity and training in examinations and testing procedures to identify cause of death
- Easily accessible electronic files for registration
- Training in stillbirth registration and classification

- Dedicated and motivated staff for registrations
- Feedback and other incentives to motivate staff
- Local adaptations of a sustainable system for registering and reporting
- Quality indicators developed for local needs
- Regional or national data collection and analysis

Appendix 2 - Egypt: Assiut University Hospital

The hospital center in Assiut is a tertiary university hospital that receives women from low to middle socioeconomic levels. In 2007, the hospital attended 13,398 deliveries and 6550 antenatal care clients. There is 50%-75% coverage of the care system in the area.

Pregnancies are captured from 22 weeks gestation. The current system can also register stillbirths from 28 weeks gestation (or 1000 g or 35 cm) including intrapartum deaths. Using this definition, the hospital stillbirth rate is 70/1000.

No specific person is responsible for reporting stillbirths in particular. However, systematic reporting on stillbirths is included in the general statistics of the delivery unit, which provides the stillbirth rate. The outcome of pregnancy is reported in the medical file by the attendant obstetrician, but these files are not easily accessed for registrations. Therefore, the hospital is moving towards introducing the recording of labor and delivery data into a computerized database. This move would facilitate data capture and strengthen the quality of data in general and in particular, the quality of reported pregnancies and stillbirths. The main challenge of such a system is sustainability within available resources. Data entry is performed by residents who need to be motivated and to see the usefulness of the work in order to achieve quality in the reporting.

The proposed system of registration could be implemented at the Assiut Hospital. An anticipated challenge would be the necessity to train data collectors in ICD-10. Potential feasible additions to the proposed dataset for monitoring includes collection and laboratory analysis of cord blood to identify blood group incompatibilities, genetic analysis, and photographs to document the findings of macroscopic exams.

Appendix 3 - Thailand: Srinagarind Hospital

Srinagarind is a 1000-bed, urban teaching hospital located in Khon Kaen in the Khon Kaen province of Thai-

land. The hospital provides comprehensive obstetric care. Each year, 2500-3000 women give birth in Srinagarind, and it provides antenatal care to 2500 women. The antenatal care clinic opens weekdays from 9:00 to noon, and the high-risk pregnancy clinic opens from 13:00 to 16:00.

The hospital's strategy is to capture pregnancies from <22 weeks and stillbirths based on the 22-week definition (500 g or 25 cm). With this definition, the stillbirth rate is 7/1000. The stillbirth capturing system identifies intrapartum deaths, which represent 3/1000 births.

Registered nurses register all births (live and stillbirth), and one senior registered nurse is responsible for reporting. There is no lower limit on registration and reporting of live births. Residents are responsible for reporting the monthly statistics in the departmental meeting. Information on all births, including complications, is entered into computer files that can be readily assessed.

The proposed system of registration could be implemented at Srinagarind Hospital, Khon Kaen University. All items are applicable in this setting would be integrated with neonatal death registrations. Additions to the dataset might include the ability to distinguish between vacuum and forceps in assisted vaginal deliveries and separate categories for maternal anemia and pre-eclampsia, preterm labor, and fetal distress.

Appendix 4 - South Africa: East London Hospital Complex

Located in East London, this urban hospital complex is a second-line birthing institution equipped with 1676 beds, of which 60 are gynecology beds and 180 obstetric beds. It receives mainly women from low socioeconomic groups who cannot afford private care. The number of births per year is 13,000-14,000, and the hospital provides antenatal care for the same population. It has high coverage of both antenatal (>80%) and intrapartum (>90%) care. The hospital uses the stillbirth definition ≥ 500 g (weight only, no gestational age or length) for registration, and the stillbirth rate ≥ 1000 g is 23/1000. The intrapartum stillbirth rate is approximately 7/1000.

A significant strength of the hospital's registration program is its participation in the well-structured national Perinatal Problem Identification Program (PPIP, <http://www.ppip.co.za>). Doctors or midwives fill in the individual perinatal death report, while a dedicated statistics nurse registers births and checks that all births recorded in the labor ward are accounted for. Data are submitted monthly to a national PPIP database. PPIP differs from the proposed classification approach in that it does not collect data specifically on intrapartum vs. antepartum

deaths, but on four categories: "stillborn, alive on admission," "fresh stillborn, dead on admission," "stillborn, admission status unknown," and "macerated stillborn." The sum of the three first categories is reported as an approximation of intrapartum death rates.

A weakness of the hospital's current system is the inability to capture deaths outside the hospital in the communities served and, thus, a lack of information on perinatal deaths occurring at home. A second weakness is the use of a manual counting system and not an electronic maternity database. The latter would be a feasible and major opportunity to improve data collection.

In this setting, there are few obstacles to capturing data on stillbirths systematically, and extending registrations to a maternity database remains a question of prioritizing resources in a setting where skilled staff shortage is the main limitation of the health care system. A maternity database would not directly lead to improved capture of stillbirths in home deliveries. Some could be captured with access to death registration data, but some are not reported at all by the families.

A specific disincentive to the registration of stillbirths in South Africa is that registered stillborn babies require a formal burial, which places a large financial burden on the family. Even in the case of in-hospital stillbirths of borderline weight, hospital staff may assist the family to avoid the cost of burial by recording the death as a miscarriage.

Authors' contributions

JFF drafted the manuscript in consultation with SJG. SJG reviewed existing classification systems in the table. AB and MM collected and drafted the experiences on data collection in Appendices 1, 2, 3 and 4. All authors edited drafts of the manuscript and read and approved the final manuscript.

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Method of delivery and pregnancy outcomes in Asia: the WHO global survey on maternal and perinatal health 2007–08

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Summary

Background There has been concern about rising rates of caesarean section worldwide. This Article reports the third phase of the WHO global survey, which aimed to estimate the rate of different methods of delivery and to examine the relation between method of delivery and maternal and perinatal outcomes in selected facilities in Africa and Latin America in 2004–05, and in Asia in 2007–08.

Methods Nine countries participated in the Asia global survey: Cambodia, China, India, Japan, Nepal, Philippines, Sri Lanka, Thailand, and Vietnam. In each country, the capital city and two other regions or provinces were randomly selected. We studied all women admitted for delivery during 3 months in institutions with 6000 or fewer expected deliveries per year and during 2 months in those with more than 6000 deliveries. We gathered data for institutions to obtain a detailed description of the health facility and its resources for obstetric care. We obtained data from women's medical records to summarise obstetric and perinatal events.

Findings We obtained data for 109 101 of 112 152 deliveries reported in 122 recruited facilities (97% coverage), and analysed 107 950 deliveries. The overall rate of caesarean section was 27·3% (n=29 428) and of operative vaginal delivery was 3·2% (n=3465). Risk of maternal mortality and morbidity index (at least one of: maternal mortality, admission to intensive care unit [ICU], blood transfusion, hysterectomy, or internal iliac artery ligation) was increased for operative vaginal delivery (adjusted odds ratio 2·1, 95% CI 1·7–2·6) and all types of caesarean section (anteartum without indication 2·7, 1·4–5·5; anteartum with indication 10·6, 9·3–12·0; intrapartum without indication 14·2, 9·8–20·7; intrapartum with indication 14·5, 13·2–16·0). For breech presentation, caesarean section, either anteartum (0·2, 0·1–0·3) or intrapartum (0·3, 0·2–0·4), was associated with improved perinatal outcomes, but also with increased risk of stay in neonatal ICU (2·0, 1·1–3·6; and 2·1, 1·2–3·7, respectively).

Interpretation To improve maternal and perinatal outcomes, caesarean section should be done only when there is a medical indication.

Funding US Agency for International Development (USAID); UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), WHO, Switzerland; Ministry of Health, Labour and Welfare of Japan; Ministry of Public Health, China; and Indian Council of Medical Research.

Introduction

Several factors, including the increased perception of safety, have contributed to a worldwide increase in rates of caesarean section.¹ In many countries, these rates have reached epidemic proportions, motivating a debate about whether the high rates are appropriate.² Unnecessary caesarean section is a classic example of the mismatch between evidence and practice in obstetrics. This debate also draws attention to the complexities that attempts to change practice entail.^{3,4} On the one hand, some are concerned about possible additional maternal and perinatal morbidity caused by unnecessary caesarean sections. On the other hand, assessment of whether the caesarean section operation poses an intrinsic risk to the mother or the baby is difficult. Ethical and practical constraints prevent assessment of intrinsic risks related to caesarean sections with use of a randomised controlled trial.

In developing countries, improvement of maternal and perinatal health strongly depends on strengthening of health systems.⁵ When resources are scarce, caesarean sections that are not medically indicated could, if done in large numbers, represent a serious resource drain. At the same time as unnecessary overuse of surgical practices is being assessed in some countries, millions of women in other countries who need these procedures do not have access to them, putting their own and their children's lives at risk.⁶

This Article reports the third phase of the WHO global survey project—a study that was implemented in the Americas (2005), Africa (2005), and Asia (2007–08) to alleviate the scarcity of information for planning and assessment of maternal and perinatal health services, specifically, intrapartum care. The survey in Latin America suggested that, at the level of facilities, increasing rates of caesarean section do not necessarily lead to

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improved outcomes and could be associated with harm.⁷ The WHO global survey in Asia aimed to obtain regional estimates of different methods of delivery in facilities, studying the relation between method of delivery and maternal and perinatal outcomes. By undertaking the study in a randomly selected number of health facilities that have not participated in research before, we aimed to develop a network with capacity to collect routine data and participate in collaborative research across countries and regions.

Methods

Study design

Methodological details of the global survey have been published elsewhere.⁸ Briefly, this is a multicountry, facility-based survey that collected data for all delivering women in randomly selected facilities worldwide. WHO subregions, classified by the number of children younger than 5 years and adult mortality rates, were used as a proxy for the burden of maternal and perinatal mortality. A stratified multistage cluster sampling design was used

to obtain a sample of countries and health institutions worldwide. From each subregion, four countries were selected, with probability proportional to population size. When a subregion had fewer than four countries, all countries within that subregion were included. This process resulted in 12 subregions having four countries each, and two subregions having three countries each.⁸ Owing to financial and practical constraints, we could not undertake the survey in developed countries of the region (unless they volunteered to—eg, Japan) and some of the selected countries (eg, Indonesia). Nine Asian countries were included: Cambodia, China, India, Japan, Nepal, Philippines, Sri Lanka, Thailand, and Vietnam. In each country, two regions or provinces, in addition to the capital city, were randomly selected by computer, with probability of selection proportional to their size. Once a province had been selected, we obtained a census of all facilities with more than 1000 births per year and those doing caesarean sections. If there were more than seven facilities, seven were randomly selected by computer, with probability of selection proportional to the number of births per year. If there were fewer than seven facilities, all were selected. In each of the selected institutions, we studied all women admitted for delivery during 3 months in institutions with 6000 or fewer expected deliveries per year and during 2 months in those with more than 6000 expected deliveries per year.

Data collection was started in China in October, 2007, and concluded in the Philippines in May, 2008. We obtained written permission from all ministries of health of the participating countries and the directors of the selected facilities. We obtained data for all individuals from medical records and did not identify participants. The Ethics Review Committee of WHO and of each country independently approved the protocol.

Data collection

We collected data for institutions and for individuals. For institutions, data included characteristics of maternal and perinatal care, including the availability of laboratory tests; anaesthesiology resources; services for intrapartum care, delivery, and care of the newborn baby; and presence or absence of basic emergency medical and obstetric care facilities, intensive care units (ICUs), and human and training resources. We gathered data only once to obtain a detailed description of the health facility and its resources for obstetric care. The hospital coordinator completed a form in consultation with the director or head of obstetrics. For individuals, we obtained data from women's medical records to complete a two-page precoded form, summarising obstetric and perinatal events. Data collected included demographic characteristics, maternal risk, current pregnancy, method of delivery, and outcomes (maternal and perinatal) up to hospital discharge. All women giving birth at the facility during the study period were included. Trained staff reviewed the medical records of all women and their

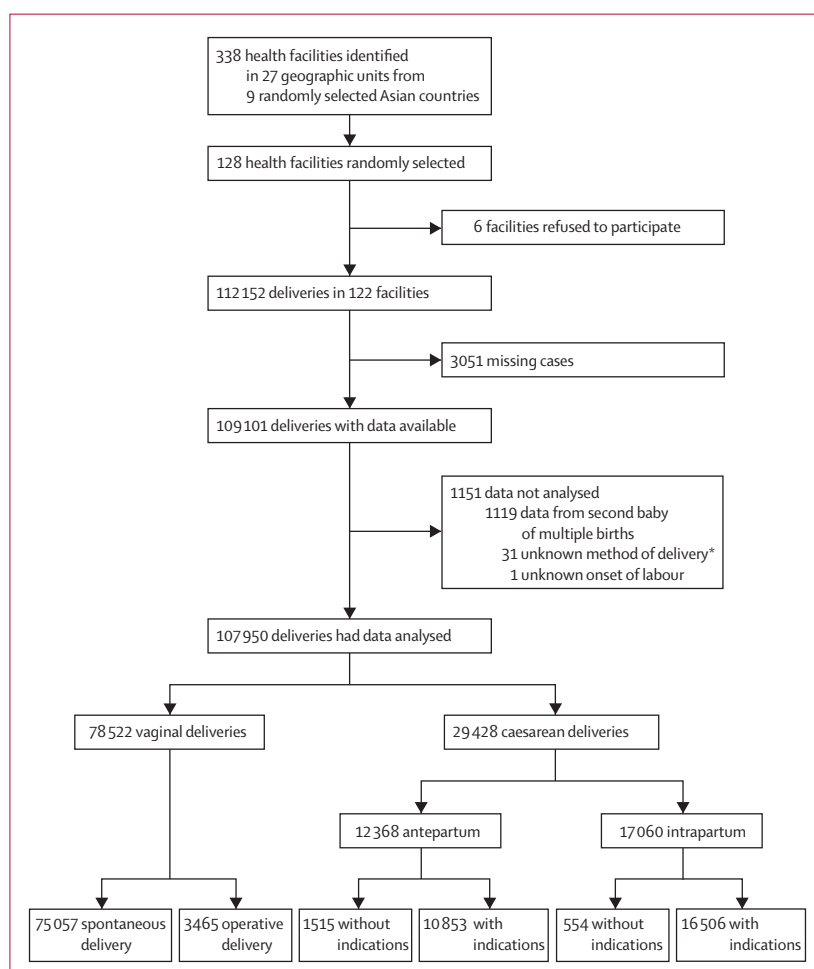


Figure 1: Study profile

*Includes 28 cases of laparotomy for uterus rupture.

	Vaginal delivery		Caesarean section				Total	
	Spontaneous	Operative	Overall	Antepartum without indications	Antepartum with indications	Intrapartum without indications	Intrapartum with indications	
Cambodia	4319 (77.6%)	431 (7.7%)	14.7%	2 (0.04%)	144 (2.6%)	12 (0.2%)	657 (11.8%)	5565 (5.2%)
China	7649 (52.6%)	179 (1.2%)	46.2%	1356 (9.3%)	2855 (19.6%)	341 (2.4%)	2161 (14.9%)	14541 (13.5%)
India	19586 (79.3%)	719 (2.9%)	17.8%	16 (0.1%)	892 (3.6%)	48 (0.2%)	3421 (13.9%)	24682 (22.9%)
Japan	2445 (74.1%)	200 (6.1%)	19.8%	2 (0.1%)	457 (13.9%)	0	196 (5.9%)	3300 (3.1%)
Nepal	6447 (75.9%)	323 (3.8%)	20.3%	3 (0.04%)	522 (6.2%)	5 (0.1%)	1189 (14.0%)	8489 (7.9%)
Philippines	10427 (78.4%)	372 (2.8%)	18.8%	5 (0.04%)	1064 (8.0%)	19 (0.1%)	1408 (10.6%)	13295 (12.3%)
Sri Lanka	9900 (65.9%)	526 (3.5%)	30.6%	83 (0.6%)	3021 (20.1%)	29 (0.2%)	1465 (9.8%)	15024 (13.9%)
Thailand	6007 (61.6%)	420 (4.3%)	34.1%	33 (0.3%)	1309 (13.4%)	15 (0.2%)	1961 (20.1%)	9745 (9.0%)
Vietnam	8277 (62.2%)	295 (2.2%)	35.6%	28 (0.2%)	576 (4.3%)	112 (0.8%)	4021 (30.2%)	13309 (12.3%)
Total	75 057 (69.5%)	3465 (3.2%)	27.3%	1515 (1.4%)	10 853 (10.1%)	554 (0.5%)	16 506 (15.3%)	107 950 (100%)

Table 1: Numbers of women by country and method of delivery

babies before discharge from the hospital, and abstracted data daily to their forms for individual data collection. The hospital coordinator supervised data collection, resolving or clarifying unclear medical notes before forms were sent for data entry. Attending staff updated incomplete records before discharge.

We developed a hospital complexity index, summarising an institution's capacity to provide different levels of care, dependent on its ratings for eight categories: building, general medical care, laboratory, anaesthesiology, screening tests, human resources, basic obstetric services, and continuous medical education. We classified hospitals without any of these services or resources as low level (rating score 0), those that had both essential and optional services and resources as high level (rating score 2), and those that did not have some of the optional services or resources, but had all essentials, as medium level (rating score 1). We judged hospitals with a total score of 9 or less of low complexity, those with scores of between 10 and 12 of medium complexity, and those with scores of 13 or more of high complexity. Criteria for data abstraction were defined in the manual of operations, which was available for staff training and monitoring of data quality, keeping to a minimum the need for judgment and interpretation. The manual contained definitions of all terms used and synonyms of medical and obstetric terms, and described questions and precoded corresponding answers.

Statistical analysis

All data were continuously entered by country data managers or hospital coordinators with a web-based system (MedSciNet AB, Stockholm, Sweden) in collaboration with WHO between October, 2007, and May, 2008. We calculated the survey coverage by comparing the number of delivery forms completed during the study period with the total number of deliveries, as independently recorded in the hospital logbooks. We used frequencies to describe methods of delivery for each country and facility characteristics, and

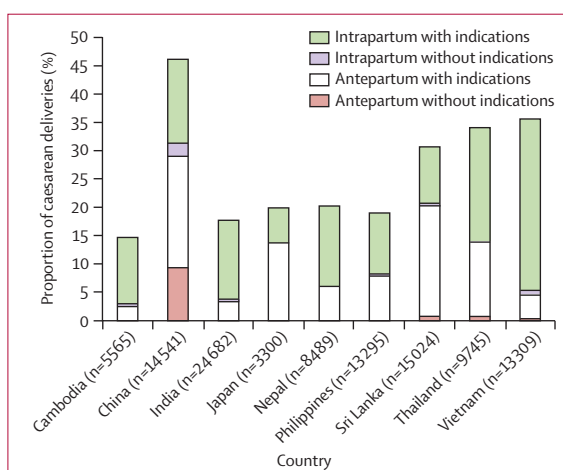


Figure 2: Proportion of caesarean deliveries by four classifications and countries

characteristics of mothers and babies for each group of delivery method. We assessed the association of each maternal outcome of death, admission to ICU, blood transfusion, hysterectomy, and mortality and morbidity index (which was defined as the presence of at least one of: maternal mortality, admission to ICU, blood transfusion, hysterectomy, or internal iliac artery ligation); and perinatal outcomes of perinatal mortality, fetal deaths, neonatal mortality up to hospital discharge, stay in neonatal ICU for 7 days or longer, and perinatal mortality and morbidity index (defined as the presence of perinatal death or stay in neonatal ICU for 7 days or longer), with methods of delivery by use of odds ratios (OR) and 95% CIs.

Univariate analysis was done separately for assessment of the association of methods of delivery and other characteristics of mothers, babies, and facilities individually on each outcome. The crude ORs were always corrected for the clustering effect of the facility. Individual-level and facility-level variables that were significantly associated with the outcome in the univariate

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	Vaginal delivery		Caesarean section				Total (n=107 950)
	Spontaneous (n=75 057)	Operative (n=3465)	Antepartum without indications (n=1515)	Antepartum with indications (n=10 853)	Intrapartum without indications (n=554)	Intrapartum with indications (n=16 506)	
General characteristics							
Marital status (single)	4973 (6.6%)	196 (5.7%)	4 (0.3%)	425 (3.9%)	7 (1.3%)	552 (3.3%)	6157 (5.7%)
Maternal age (years)							
≤16	550 (0.7%)	19 (0.6%)	0	22 (0.2%)	1 (0.2%)	63 (0.4%)	655 (0.6%)
17–34	68 713 (91.6%)	3091 (89.2%)	1378 (91.0%)	8841 (81.5%)	500 (90.3%)	14 772 (89.5%)	97 295 (90.2%)
≥35	5780 (7.7%)	355 (10.2%)	137 (9.0%)	1989 (18.3%)	53 (9.5%)	1667 (10.1%)	9981 (9.3%)
Primigravida	32 479 (43.3%)	1948 (56.2%)	671 (44.3%)	3372 (31.1%)	251 (45.3%)	7743 (46.9%)	46 464 (43.0%)
Last pregnancy							
Last baby birthweight (previous delivery [g])							
<1500	904 (1.2%)	91 (2.6%)	1 (0.1%)	161 (1.5%)	0	93 (0.6%)	1250 (1.2%)
≥1500–2499	9292 (12.3%)	501 (14.5%)	26 (1.7%)	1486 (13.7%)	22 (3.9%)	1654 (10.0%)	12 981 (12.0%)
≥2500–3999	63 900 (85.2%)	2808 (81.1%)	1383 (91.3%)	8664 (79.8%)	510 (92.1%)	14 040 (85.1%)	91 305 (84.6%)
≥4000–4499	873 (1.2%)	56 (1.6%)	95 (6.3%)	457 (4.2%)	21 (3.8%)	621 (3.8%)	2123 (2.0%)
≥4500	69 (0.1%)	6 (0.2%)	9 (0.6%)	83 (0.8%)	1 (0.2%)	87 (0.5%)	255 (0.2%)
Caesarean delivery in the last pregnancy	1034 (1.4%)	127 (3.7%)	43 (2.8%)	3996 (36.8%)	21 (3.8%)	3347 (20.3%)	8568 (7.9%)
Complications during current pregnancy							
Prelabour rupture of membranes	8388 (11.2%)	425 (12.3%)	129 (8.5%)	732 (6.7%)	112 (20.2%)	3100 (18.8%)	12 886 (11.9%)
Pregnancy-induced hypertension	2158 (2.9%)	222 (6.4%)	38 (2.5%)	838 (7.7%)	16 (2.9%)	845 (5.1%)	4117 (3.8%)
Pre-eclampsia	1096 (1.5%)	134 (3.9%)	7 (0.5%)	543 (5.0%)	1 (0.2%)	517 (3.1%)	2298 (2.1%)
Eclampsia	183 (0.2%)	36 (1.0%)	1 (0.1%)	73 (0.7%)	0	96 (0.6%)	389 (0.4%)
Breech or other non-cephalic presentation	805 (1.1%)	725 (20.9%)	0	1637 (15.1%)	0	2172 (13.2%)	5339 (5.0%)
Referred for complication related to pregnancy or delivery	13 719 (18.3%)	698 (20.1%)	100 (6.6%)	2781 (25.6%)	49 (8.8%)	2828 (17.1%)	20 175 (18.7%)
Data are number (% of country total) for method of delivery columns and (% of study total) for total column.							
Table 2: Characteristics of women classified by method of delivery							

Data are number (% of country total) for method of delivery columns and (% of study total) for total column.

Table 2: Characteristics of women classified by method of delivery

analysis ($p<0.05$) were successively included in a multivariate model. In the multivariate analysis, each model of the outcomes of interest included method of delivery defined in six categories: vaginal spontaneous (reference category); operative vaginal; antepartum caesarean delivery with and without indications; and intrapartum caesarean delivery with and without indications, and the variables found to be significant in the univariate analyses. Variables for both individuals and facilities that did not show significance at the 5% level in the resulting model were then removed one by one until all remaining variables were significant. Gestational age was always included irrespective of statistical significance when we considered perinatal outcomes. For all models fitted, we used generalised linear and latent mixed models (GLLMM) for the multilevel analysis by using procedure GLIMMIX in SAS (version 9.1). The procedure accounted for clustering effects within facilities. The multilevel analysis was also done for perinatal outcomes in subgroups of fetal presentations (cephalic, breech, and others). Risks of maternal and perinatal outcomes associated with method of delivery were presented by adjusted ORs with corresponding 95% CIs.

Role of the funding sources

The sponsors of the study had no role in study design, data collection, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the study profile. In the nine randomly selected Asian countries, we selected 27 geographical units. There were 388 health facilities in these units, of which we randomly selected 128 facilities. Six facilities declined to participate, leaving 122 in the survey. 112 152 deliveries were reported in these 122 facilities during the study period. Our survey collected data for 109 101 deliveries (97% coverage). We checked the data quality by randomly selecting 5% of the records and asking the hospital coordinators to extract the same data from medical records again, and compared these data with the original record. The mean agreement was 92% (range 81–98). We excluded 31 patients with unknown method of delivery, 1119 second babies of multiple births, and one with unknown onset of labour, leaving 107 950 analysable deliveries.

China, India, and the Philippines had the highest numbers of facilities (seven per province), whereas India, Sri Lanka, and China had the highest numbers of deliveries (table 1). 84 (69%) facilities were in urban areas and 104 (85%) were in the public system. Most of the hospitals were secondary or tertiary referral hospitals; however, 83 (68%) had low facility complexity resources. 87 (71%) hospitals had anaesthesiology resources 24 h per day in the facility, and in 75 (62%), financial incentives were offered for undertaking caesarean section. The overall rate of caesarean section of this survey in Asia was 27·3%. China had the highest overall rate followed by Vietnam, Thailand, and Sri Lanka (table 1). China also had the highest rate of caesarean section without indication (11·7%), followed by Vietnam (1·0%), Sri Lanka (0·8%), and Thailand (0·5%; table 1 and figure 2). Since the pattern of caesarean section was substantially different in China from the other countries (figure 2), we undertook a sensitivity analysis for the maternal and newborn outcomes, excluding data from China. We noted no changes to the results (data not shown), and the results are reported for all nine countries together. The commonly reported indications for caesarean section were previous caesarean section (24·2%), cephalopelvic disproportion (22·6%), fetal distress (20·5%), and breech or other abnormal presentation (12·5%).

Table 2 shows characteristics of women by method of delivery. We noted a higher proportion of single marital status and very low birthweight infant (<1500 g) in women who delivered vaginally than in those who delivered by caesarean section. Delivery by caesarean section in the last pregnancy was more common in women who delivered by caesarean section than in those who had vaginal delivery (table 2). The rates of complications during current pregnancy were similar between women who delivered vaginally or by caesarean section (table 2).

For maternal mortality, only operative vaginal delivery had significantly increased risk compared with spontaneous vaginal deliveries (adjusted OR 3·1, 95% CI 1·5–6·5). The risk for antepartum caesarean section without indication could not be estimated because there were no maternal deaths in this group. Operative vaginal delivery and all types of caesarean section had significantly increased risk of admission to ICU compared with spontaneous vaginal delivery (table 3). Operative vaginal delivery, antepartum caesarean section with indications, and intrapartum caesarean section with and without indication had significantly increased risks of blood transfusion compared with spontaneous vaginal delivery (table 3). The risk of hysterectomy was increased in mothers who delivered by operative vaginal delivery, antepartum caesarean section with indications, and intrapartum caesarean section with indications (table 3). We recorded no cases of hysterectomy in women who delivered by antepartum caesarean section without indications and intrapartum caesarean section without indications, so

	n/N (%)	Adjusted OR (95%CI)
Death*		
Spontaneous (reference)	53/75 057 (0·1%)	1
Operative vaginal delivery	9/3465 (0·3%)	3·1 (1·5–6·5)
Antepartum CS without indications	0/1515	..
Antepartum CS with indications	11/10 853 (0·1%)	1·1 (0·5–2·3)
Intrapartum CS without indications	1/554 (0·2%)	4·8 (0·6–36·0)
Intrapartum CS with indications	23/16 506 (0·1%)	1·6 (0·9–2·8)
Admission to ICU†		
Spontaneous (reference)	442/75 057 (0·5%)	1
Operative vaginal delivery	76/3465 (2·0%)	2·4 (1·8–3·3)
Antepartum CS without indications	5/1515 (0·3%)	9·9 (3·8–25·8)
Antepartum CS with indications	391/10 853 (3·6%)	42·8 (34·5–53·1)
Intrapartum CS without indications	35/554 (6·2%)	67·0 (42·0–106·7)
Intrapartum CS with indications	1489/16 506 (9·0%)	55·7 (47·1–65·8)
Blood transfusion‡		
Spontaneous (reference)	785/75 057 (1·0%)	1
Operative vaginal delivery	78/3465 (2·3%)	2·1 (1·6–2·8)
Antepartum CS without indications	3/1515 (0·3%)	0·8 (0·3–2·6)
Antepartum CS with indications	352/10 853 (3·2%)	4·1 (3·4–4·8)
Intrapartum CS without indications	7/554 (1·4%)	3·9 (1·8–8·5)
Intrapartum CS with indications	541/16 506 (3·3%)	4·7 (4·1–5·3)
Hysterectomy§		
Spontaneous (reference)	28/75 057 (0·04%)	1
Operative vaginal delivery	4/3465 (3·3%)	2·8 (0·9–7·9)
Antepartum CS without indications	0/1515	..
Antepartum CS with indications	35/10 853 (0·3%)	6·9 (4·1–11·6)
Intrapartum CS without indications	0/554	..
Intrapartum CS with indications	37/16 506 (0·2%)	5·8 (3·5–9·6)
Maternal mortality and morbidity index¶		
Spontaneous (reference)	1215/75 057 (1·6%)	1
Operative vaginal delivery	146/3465 (4·2%)	2·1 (1·7–2·6)
Antepartum CS without indications	9/1515 (0·6%)	2·7 (1·4–5·5)
Antepartum CS with indications	744/10 853 (6·9%)	10·6 (9·3–12·0)
Intrapartum CS without indications	40/554 (7·2%)	14·2 (9·8–20·7)
Intrapartum CS with indications	1947/16 506 (11·8%)	14·5 (13·2–16·0)

OR=odds ratio. CS=caesarean section. ICU=intensive care unit. *Adjusted for malaria, severe anaemia, other medical disorders, any condition suggesting HIV/AIDS, pre-eclampsia, eclampsia, suspected fetal growth impairment, vaginal bleeding in second half of pregnancy, and referred for complication related to pregnancy or delivery. †Adjusted for maternal age, year of education, birthweight, HIV, chronic hypertension, cardiac/renal diseases, malaria, severe anaemia, other medical disorders, prelabour rupture of membranes, pregnancy-induced hypertension, pre-eclampsia, eclampsia, vaginal bleeding in second half of pregnancy, referred for complication related to pregnancy or delivery, and country. ‡Adjusted for maternal age, year of education, primiparous, birthweight, cervix surgery, chronic respiratory disease, sickle-cell anaemia, severe anaemia, other medical diseases, pregnancy-induced hypertension, pre-eclampsia, eclampsia, vaginal bleeding in second half of pregnancy, referred for complication related to pregnancy or delivery, and country. §Adjusted for chronic hypertension, severe anaemia, and vaginal bleeding in second half of pregnancy. ¶Maternal mortality and morbidity index=death or admission to ICU, blood transfusion, hysterectomy, or internal iliac artery ligation. Adjusted for maternal age, year of education, primiparous, birthweight, history of neonatal death or stillbirth, HIV, chronic hypertension, cardiac/renal diseases, sickle-cell anaemia, severe anaemia, other medical disorders, prelabour rupture of membranes, pregnancy-induced hypertension, pre-eclampsia, eclampsia, vaginal bleeding in second half of pregnancy, any antenatal antibiotic treatment, referred for complication related to pregnancy or delivery, and country.

Table 3: Risk of maternal mortality and morbidity by method of delivery

the risk could not be estimated. Operative vaginal delivery and all types of caesarean section were associated with significantly increased risk of maternal mortality and morbidity index compared with spontaneous vaginal

delivery (table 3). Intrapartum caesarean section (both with and without indications) had higher risk of maternal

mortality and morbidity than did antepartum caesarean section (table 3). Deliveries by all types of caesarean section had significantly increased risks of maternal mortality and morbidities except for perineal tears of third and fourth degree, for which as expected caesarean section had a protective effect compared with vaginal delivery (data not shown).

Risk of perinatal mortality was significantly increased compared with spontaneous vaginal delivery in infants born by operative vaginal delivery and intrapartum caesarean section with indications (table 4). Only infants delivered by antepartum caesarean section with indications had a significantly lower risk of fetal death than those born vaginally, whereas risk of fetal death did not differ significantly for other methods of delivery compared with spontaneous vaginal delivery (table 4). For neonatal mortality up to hospital discharge, infants born by operative vaginal delivery, antepartum caesarean section with indications, and intrapartum caesarean section with indications had significantly increased risk compared with spontaneous vaginal delivery (table 4). We recorded no cases of neonatal mortality up to hospital discharge for women delivering by caesarean section without indication, and the risk compared with spontaneous vaginal delivery could not be estimated.

Infants born by operative vaginal delivery and intrapartum and antepartum caesarean section with indications had significantly increased risk of stay for 7 days or longer in neonatal ICU compared with spontaneous vaginal delivery (table 4). Operative vaginal delivery and antepartum and intrapartum caesarean section with indications had significantly increased risk of perinatal mortality and morbidity index (table 4). For breech and other abnormal presentation, caesarean section with indication, either antepartum or intrapartum, significantly reduced risk of perinatal mortality but had significantly increased risk of stay in neonatal ICU for 7 days or longer (table 5).

Discussion

In the 122 Asian health facilities studied, more than one in four women underwent caesarean section. Facilities in China, Sri Lanka, Vietnam, and Thailand had higher aggregated rates of caesarean section than did those in Cambodia, India, Japan, Nepal, and the Philippines. Operative vaginal delivery and caesarean section were independently associated with increased risk of maternal mortality and morbidity index. Caesarean section without a medical indication was associated with increased risk of maternal mortality and morbidity. Caesarean section for breech presentation was associated with improved perinatal outcomes.

With use of a slightly different analytical approach, this survey confirms the findings of the previous survey undertaken in Latin America.⁹ Together these findings provide strong multiregional support for the recommendation of avoiding unnecessary caesarean

	n/N (%)	Adjusted OR (95%CI)
Perinatal mortality*		
Spontaneous (reference)	1072/75 057 (1.4%)	1
Operative vaginal delivery	126/3465 (3.6%)	1.6 (1.2-2.0)
Antepartum CS without indications	1/1515 (0.1%)	0.3 (0.04-2.3)
Antepartum CS with indications	143/10 853 (1.3%)	1.1 (0.9-1.3)
Intrapartum CS without indications	0/554	..
Intrapartum CS with indications	284/16 506 (1.7%)	1.5 (1.2-1.7)
Fetal death†		
Spontaneous (reference)	673/74 945 (0.9%)	1
Operative vaginal delivery	68/3448 (2.0%)	1.1 (0.8-1.6)
Antepartum CS without indications	1/1515 (0.1%)	0.4 (0.06-3.2)
Antepartum CS with indications	61/10 853 (0.6%)	0.6 (0.5-0.8)
Intrapartum CS without indications	0/554	..
Intrapartum CS with indications	130/16 504 (0.8%)	0.8 (0.6-1.0)
Neonatal mortality up to hospital discharge‡		
Spontaneous (reference)	399/73 726 (0.5%)	1
Operative vaginal delivery	58/3320 (1.8%)	2.5 (1.7-3.7)
Antepartum CS without indications	0/1514	..
Antepartum CS with indications	82/10 767 (0.8%)	1.7 (1.3-2.3)
Intrapartum CS without indications	0/580	..
Intrapartum CS with indications	154/16 319 (1.0%)	2.6 (2.1-3.2)
Stay for ≥7 days in neonatal ICU§		
Spontaneous (reference)	1092/75 057 (1.5%)	1
Operative vaginal delivery	110/3465 (3.2%)	1.9 (1.5-2.4)
Antepartum CS without indications	5/1515 (0.3%)	0.4 (0.2-1.1)
Antepartum CS with indications	458/10 853 (4.2%)	2.4 (2.0-2.8)
Intrapartum CS without indications	5/554 (0.9%)	1.3 (0.5-3.1)
Intrapartum CS with indications	436/16 506 (2.6%)	2.4 (2.1-2.8)
Perinatal mortality and morbidity index¶		
Spontaneous (reference)	2117/75 057 (2.8%)	1
Operative vaginal delivery	232/3465 (6.7%)	1.9 (1.6-2.3)
Antepartum CS without indications	6/1515 (0.4%)	0.4 (0.2-0.9)
Antepartum CS with indications	593/10 853 (5.5%)	1.9 (1.7-2.2)
Intrapartum CS without indications	5/554 (0.9%)	0.9 (0.4-2.3)
Intrapartum CS with indications	707/16 479 (4.3%)	2.1 (1.9-2.3)

OR=odds ratio. CS=caesarean section. ICU=intensive care unit. *Adjusted for year of education, birthweight, history of neonatal death or stillbirth, severe anaemia, pre-eclampsia, eclampsia, vaginal bleeding in second half of pregnancy, breech or other non-cephalic presentation, referred for complication related to pregnancy or delivery, induced labour, country, and gestational age. †Adjusted for year of education, birthweight, sickle-cell anaemia, severe anaemia, eclampsia, suspected fetal growth impairment, vaginal bleeding in second half of pregnancy, breech or other non-cephalic presentation, referred for complication related to pregnancy or delivery, and gestational age. ‡Adjusted for year of education, birthweight, breech or other non-cephalic presentation, referred for complication related to pregnancy or delivery, country, and gestational age. §Adjusted for year of education, birthweight, caesarean delivery, chronic hypertension, condyloma acuminatum, other medical disorders, prelabour rupture of membranes, pregnancy-induced hypertension, pre-eclampsia, eclampsia, suspected fetal growth impairment, vaginal bleeding in second half of pregnancy, any antenatal antibiotic treatment, breech or other non-cephalic presentation, referred for complication related to pregnancy or delivery, induced labour, country, and gestational age. ¶Perinatal mortality and morbidity index=perinatal mortality or stay for 7 or more days in neonatal ICU. Adjusted for year of education, birthweight, history of neonatal death or stillbirth, caesarean delivery, chronic hypertension, chronic respiratory disorders, diabetes mellitus, condyloma acuminatum, other medical disorders, prelabour rupture of membranes, pregnancy-induced hypertension, pre-eclampsia, eclampsia, suspected fetal growth impairment, vaginal bleeding in second half of pregnancy, any antenatal antibiotic treatment, breech or other non-cephalic presentation, referred for complication related to pregnancy or delivery, country, and gestational age.

Table 4: Perinatal outcomes for singleton and first child of multiple births by method of delivery

sections. A randomised controlled trial¹⁰ to assess the benefits and risks of caesarean section might not be a realistic approach in view of the immediate and long-term physical and psychological effects of different methods of delivery on the woman and her baby and the lack of agreement between health professionals. In the absence of a randomised trial, we have to rely on observational studies to elucidate various benefits and risks of this operation. Intrinsic risk associated with the caesarean section operation is not easy to separate from the medical and obstetrical indications that lead to the procedure. In the previous survey, the intrinsic risk was investigated by dividing the method of delivery into three categories: vaginal, elective caesarean section, and intrapartum caesarean section with elective caesarean section as a proxy. We identified six categories as described in the results. Assisted vaginal delivery represents a high-risk situation, and combination of such deliveries with spontaneous vaginal deliveries as the reference group might not be appropriate. Second, we noticed that several births that were recorded as elective had an indication for caesarean section. The group with no medical indication therefore is probably a more appropriate group to assess the intrinsic risk associated with this procedure.

The most important finding of the survey is the increased risk of maternal mortality and severe morbidity, which was analysed as a composite outcome (the maternal mortality and morbidity index), in women who undergo caesarean section with no medical indication. The findings for the individual outcomes that make up the composite outcome suggest that the increased risk is mainly attributable to increased admission to ICU and blood transfusion. Although we acknowledge that both ICU admission and blood transfusion depend on the availability of those services and the potentially differing thresholds for giving blood and for admission of women to ICU or referral to higher levels of care, this outcome is nevertheless important.

Quantification of the risk across facilities and countries might not be appropriate because there will be differences from setting to setting. However, the results show that women receiving the operation are at increased risk of adverse events. We can therefore conclude that women who choose to have caesarean section, and the doctors who recommend the operation with no medical indication, have to make that decision with the understanding of the increased risks. The procedure also costs more than does a vaginal birth. In the UK, each additional vaginal birth instead of caesarean section would save more than £1200.¹¹ The costs include actual direct cost, use of operating theatre facilities, use of anaesthesia, human resources (theatre nurses, anaesthesiologists), and use of postoperative facilities. In low-income countries with an unmet need for caesarean section, the issue of this procedure being a resource drain is even more important than it is in high-income countries. If this operation is limited to medical

	n/N (%)	Adjusted OR (95%CI)
Cephalic presentation		
Perinatal mortality*		
Spontaneous (reference)	914/74 250 (1.2%)	1
Operative vaginal delivery	38/2740 (1.4%)	2.0 (1.4–2.9)
Antepartum CS without indications	1/1515 (0.1%)	0.3 (0.05–2.5)
Antepartum CS with indications	115/9213 (1.3%)	1.3 (1.0–1.7)
Intrapartum CS without indications	0/554	..
Intrapartum CS with indications	206/14 333 (1.4%)	1.9 (1.6–2.2)
Fetal death†		
Spontaneous (reference)	557/74 146 (0.8%)	1
Operative vaginal delivery	21/2737 (0.8%)	1.6 (1.0–2.6)
Antepartum CS without indications	1/1515 (0.1%)	0.5 (0.06–3.5)
Antepartum CS with indications	50/9213 (0.5%)	0.9 (0.6–1.2)
Intrapartum CS without indications	0/554	..
Intrapartum CS with indications	85/14 332 (0.6%)	1.1 (0.8–1.4)
Neonatal mortality up to hospital discharge‡		
Spontaneous (reference)	357/73 111 (0.5%)	1
Operative vaginal delivery	17/2705 (0.6%)	2.5 (1.5–4.4)
Antepartum CS without indications	0/1514	..
Antepartum CS with indications	65/9145 (0.7%)	2.0 (1.4–2.7)
Intrapartum CS without indications	0/554	..
Intrapartum CS with indications	121/14 214 (0.9%)	3.1 (2.4–4.0)
Stay for ≥7 days in neonatal ICU§		
Spontaneous (reference)	1067/74 250 (1.4%)	1
Operative vaginal delivery	72/2740 (2.6%)	2.3 (1.7–3.0)
Antepartum CS without indications	5/1515 (0.3%)	0.4 (0.2–1.1)
Antepartum CS with indications	381/9213 (4.1%)	2.4 (2.0–2.8)
Intrapartum CS without indications	5/554 (0.9%)	1.3 (0.5–3.2)
Intrapartum CS with indications	346/14 333 (2.4%)	2.4 (2.1–2.8)
Perinatal mortality and morbidity index¶		
Spontaneous (reference)	1938/74 250 (2.6%)	1
Operative vaginal delivery	108/2740 (3.9%)	2.2 (1.8–2.8)
Antepartum CS without indications	6/1515 (0.4%)	0.4 (0.2–1.0)
Antepartum CS with indications	489/9213 (5.3%)	2.1 (1.8–2.4)
Intrapartum CS without indications	5/554 (0.9%)	1.0 (0.4–2.4)
Intrapartum CS with indications	541/14 333 (3.8%)	2.3 (2.0–2.5)

(Continues on next page)

indications and unnecessary use is avoided, resources will be used for a need and will not be taken from other parts of the health system.

The situation regarding potential risk of caesarean section is less clear when the woman has medical or obstetric indications for the procedure. We made several statistical adjustments to try to separate the possible effect of caesarean section in the maternal and perinatal outcomes. After all adjustments, women with medical indications for the operation had an increased risk of morbidity and mortality. One possible interpretation is that the increased risk results from the interaction between baseline morbidity and the morbidity specific to caesarean section. Alternatively, the statistical adjustment might have been unable to isolate the effect of the baseline morbidity—ie, the observed increased risk of

	n/N (%)	Adjusted OR (95%CI)
(Continued from previous page)		
Breech and other presentations		
Perinatal mortality		
Spontaneous (reference)	158/805 (19.6%)	1
Operative vaginal delivery	88/725 (12.1%)	0.6 (0.4–0.9)
Antepartum CS with indications	28/1637 (1.7%)	0.2 (0.1–0.3)
Intrapartum CS with indications	78/2172 (3.6%)	0.3 (0.2–0.4)
Fetal death**		
Spontaneous (reference)	116/797 (14.6%)	1
Operative vaginal delivery	47/711 (6.6%)	0.5 (0.3–0.7)
Antepartum CS with indications	11/1637 (0.7%)	0.07 (0.03–0.1)
Intrapartum CS with indications	45/2171 (2.1%)	0.2 (0.1–0.3)
Neonatal mortality up to hospital discharge††		
Spontaneous (reference)	42/613 (6.9%)	1
Operative vaginal delivery	41/615 (6.7%)	1.3 (0.7–2.3)
Antepartum CS with indications	17/1619 (1.1%)	0.4 (0.2–0.9)
Intrapartum CS with indications	33/2104 (1.6%)	0.6 (0.3–1.0)
Stay for ≥7 days in neonatal ICU‡‡		
Spontaneous (reference)	25/805 (3.1%)	1
Operative vaginal delivery	38/725 (5.2%)	1.7 (1.0–3.1)
Antepartum CS with indications	77/1637 (4.7%)	2.0 (1.1–3.6)
Intrapartum CS with indications	90/2172 (4.1%)	2.1 (1.2–3.7)
Perinatal mortality and morbidity index§§		
Spontaneous (reference)	179/805 (22.2%)	1
Operative vaginal delivery	124/725 (17.1%)	0.7 (0.5–1.0)
Antepartum CS with indications	104/1637 (6.4%)	0.4 (0.3–0.6)
Intrapartum CS with indications	166/2172 (7.6%)	0.6 (0.4–0.8)

OR=odds ratio. CS=caesarean section. ICU=intensive care unit. *Adjusted for year of education, birthweight of previous baby, history of neonatal death or stillbirth, severe anaemia, pre-eclampsia, eclampsia, vaginal bleeding in second half of pregnancy, referred for complication related to pregnancy or delivery, induced labour, country, and gestational age. †Adjusted for year of education, birthweight of previous baby, sickle-cell anaemia, severe anaemia, eclampsia, suspected fetal growth impairment, vaginal bleeding in second half of pregnancy, referred for complication related to pregnancy or delivery, incentive for caesarean section, and gestational age. ‡Adjusted for year of education, birthweight of previous baby, referred for complication related to pregnancy or delivery, country, and gestational age. §Adjusted for year of education, birthweight of previous baby, previous caesarean delivery, chronic hypertension, diabetes mellitus, condyloma acuminatum, other medical disorders, prelabour rupture of membranes, pregnancy-induced hypertension, pre-eclampsia, eclampsia, suspected fetal growth impairment, any antenatal antibiotic treatment, referred for complication related to pregnancy or delivery, induced labour, country, and gestational age. ¶Perinatal mortality and morbidity index=perinatal mortality or stay for 7 days or more in neonatal ICU. Adjusted for maternal age, year of education, birthweight, cervix surgery, chronic hypertension, chronic respiratory disorders, diabetes mellitus, severe anaemia, condyloma acuminatum, other medical disorders, prelabour rupture of membranes, pregnancy-induced hypertension, pre-eclampsia, eclampsia, suspected fetal growth impairment, vaginal bleeding in second half of pregnancy, any antenatal antibiotic treatment, referred for complication related to pregnancy or delivery, country, and gestational age. ||Adjusted for fistula, eclampsia, vaginal bleeding in second half of pregnancy, referred for complication related to pregnancy or delivery, country, and gestational age. **Adjusted for sickle-cell anaemia, vaginal bleeding in second half of pregnancy, referred for complication related to pregnancy or delivery, and gestational age. ††Adjusted for referred for complication related to pregnancy or delivery, induced labour, and gestational age. ‡‡Adjusted for condyloma acuminatum, prelabour rupture of membranes, vaginal bleeding in second half of pregnancy, any antenatal antibiotic treatment, country, and gestational age. §§Adjusted for birthweight, fistula, prelabour rupture of membranes, eclampsia, vaginal bleeding in second half of pregnancy, referred for complication related to pregnancy or delivery, induced labour, country, and gestational age.

Table 5: Perinatal outcomes for singleton and first child of multiple births by fetal presentation at delivery and method of delivery

mortality and morbidity could be attributed to the baseline conditions that caused the procedure to be undertaken. We detected a similar relation for assisted vaginal deliveries.

Findings from our survey confirm the protective effect of caesarean section on perinatal mortality for cases of breech or other presentations.¹² This result should be considered as additional evidence for strongly recommending avoidance of vaginal deliveries for breech presentations, while promoting the use of external cephalic version for term breech presentation even if the woman is already in labour.¹³

This study has several strengths. First, it is one of the largest observational studies to address the issue of benefits and harms of caesarean section, complementing the earlier surveys undertaken in Latin America^{7,9} and Africa (unpublished). Second, the random selection of two provinces in addition to the capital province, and then random selection of participating facilities with more than 1000 deliveries per year, ensured avoidance of selection bias. A secondary aim of the project was to strengthen the capacity of a network of health facilities in routine data collection and collaborative research. The random selection process was crucial in working with facilities that had not previously participated in research projects. The high data-extraction quality suggested by the random data checks was very encouraging. In several participating countries, including China and India, data were entered online within facilities, which helped with the resolution of data queries. Afghanistan and Pakistan have been added to this network of facilities in 24 countries where the survey has been undertaken, and these 26 countries will implement the next survey that will focus on maternal and neonatal near miss in the next phase of the project in 2010–11.

Our study has some limitations. First, we had information about mortality and morbidities only until discharge from hospital; some outcomes might therefore have been underestimated, especially for women delivering vaginally who are usually discharged earlier than women having caesarean section. The calculated odds ratio might overestimate the risk of caesarean section. Although we had adjusted for many potential confounding factors, there might be some other factors that we did not have information about and could not adjust for. Second, data were abstracted from the patients' records. We were not able to confirm the absence of some of the risk factors if they had not been recorded. Third, our survey included only hospitals with caesarean facilities having 1000 or more deliveries every year. The results therefore cannot be generalised to smaller facilities. The results, especially rates of caesarean section, should not be regarded as representative rates and outcomes for entire countries or regions.

In view of the strengths and the limitations, our results are corroborated by other observational studies assessing the risks of caesarean section for mothers¹⁴ and infants from different settings.¹⁵ We conclude that caesarean section should be done only when there is a medical indication to improve the outcome for the mother or the baby. Women and their carers who plan to undertake

caesarean section delivery should discuss the potential risks to make an informed decision if they still wish to have a caesarean delivery.

Contributors

PL, ML, AMG, and JPS coordinated the study. EF participated in the preparatory activities, developing the study materials, and site visits. JV was the lead investigator in the first phase of the project undertaken in Latin America and Africa. In the Asia survey, JV supported the preparatory activities such as modifications in the forms, manuals, and training planning. PL, ML, AMG and JPS planned and undertook the analysis and wrote the report with input from all country investigators and GC (regional coordinator of the Latin American survey). KB-T undertook site visits, training, and contributed to the writing of the report. PR, GY, KChu, MR, NDH, RM, KChe, TR, DEA, ST, NS, MF, HTB, VU, and MJVC contributed to study design, data collection, data analysis, data interpretation, and writing of the report. All authors read and approved the final report.

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Conflicts of interest

We declare that we have no conflicts of interest.

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Maternal and fetal mortality and complications associated with cesarean section deliveries in teaching hospitals in Asia

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Abstract

Aim: To compare the mortality, morbidity of emergency and elective cesarean section with vaginal delivery among Asian teaching hospitals

Methods: Hospital based prospective study at 12 centers of 9 countries.

Results: 12 591 vaginal deliveries, 3062 elective and 4328 emergency cesarean section were followed up to 5 days postpartum. Maternal deaths (95% CI) per 1000 births among vaginal deliveries being 0.47 (0.17, 1.03) was not significantly different from 0.31 (0.01, 1.73) of elective cesarean section and both rates were significantly lower than 2.87 (1.53, 4.91) per 1000 births of emergency section. The vaginal delivery group had significantly lower incidences of all major complication except significantly higher chance of secondary operations and non-significantly different risk for endometritis. Corresponding neonatal mortality per 1000 deliveries among the three groups were 7 (5.6, 8.6), 2.2 (0.9, 4.6) and 12.4 (9.3, 16.2) ($P < 0.001$). Vaginal delivery also had higher rates of severe asphyxia and palsy than elective cesarean section.

Conclusion: Maternal complications were increased by cesarean delivery but elective section may reduce neonatal complication.

Key words: cesarean section, maternal complications, neonatal complications, neonatal mortality, vaginal delivery.

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Introduction

For more than two decades, the rates of Cesarean Section (CS) have been increasing in both developed and most developing countries despite the World Health Organization's recommendation in 1985 which stated 'There is no justification for any region to have cesarean section rates higher than 10–15%'.¹

Although intended to reduce maternal and fetal morbidity and mortality² rising rates of CS may, however, increase adverse outcomes and place a considerable burden on health services. Adverse outcomes include wound infection, puerperal sepsis, hemorrhage and blood transfusion, anesthesia, pulmonary embolism, intraoperative trauma and fetal injury in the short term and repeat CS in subsequent pregnancies with additional risks of uterine rupture, excess blood loss, difficulties in delivering the neonate, dense adhesions, placenta accrete and hysterectomy.^{3–7} Cesarean section delivery is intended to reduce maternal and fetal mortality and with high birth rates and the limited obstetric health resources of Asian developing countries, such information is needed on its prevalence and complications for policy makers, care providers and the public before any rational guidelines for good clinical practice with regard to CS can be developed.

CS rates have increased over the past two decades and the global rate has been estimated as 15%⁷ and in Australia from less than 20% in 1993 to 29% in 2004.⁸

Similar increases in CS rates have been observed in many developing countries, however, with considerable variation both within and between countries. In South America, Brazil and Chile head the league table where CS accounts for nearly 40% and 42%, respectively, of births.⁹

The average CS rate in Southern and Eastern Asia is 15.9% with China and Hong Kong SAR with the highest estimate rates of 40.5% and 27.4%, respectively.⁷ CS rates in Nepal and Cambodia have been reported as low as 1% which are comparable to a number of other least developed countries in Central Africa. In Thailand, the mean CS rate in 1999 was 24.48 and 22% in the general, private and university hospitals, respectively.¹⁰ In Nepal, between 1997 and 2002, the overall CS rate was 9.4% in a university teaching hospital.¹¹ Rates in a maternity hospital in Mumbai, India increased from 1.9% to 16% between 1957 and 1998 with the greatest increase in the last decade.¹² In a survey of 30 medical colleges and teaching hospitals in India, it was found that the overall rate increased from 21.8% in 1993–1994 to 25.4% in 1998–1999.¹³ CS rates in

the private sector in Madras(Chennai) between 1997 and 1999 have been reported as high as 47%.¹⁴

Apart from the rates quoted in these reviews, there has been little regional information from developing countries in Southern and Eastern Asia on the morbidity, mortality and economic consequences of these rising rates of CS. With high birth rates in most of these countries and limited health resources, such information is needed for policy makers, healthcare providers and the public before decisions can be made on strategies to reduce the rates without compromising maternal and neonatal morbidity and mortality statistics.

With this in mind, the WHO's Special Programme on Research, Development, and Research Training in Human Reproduction initiated a multicenter study involving 12 medical schools and research institutes in nine Southern and Eastern Asian developing countries. The objectives of the study were to compare the mortality, morbidity and the economics of emergency and elective CS with vaginal delivery.

This paper will focus on the morbidity and mortality aspects and a subsequent paper will address the economic issues.

Materials and Methods

Study design

This was a prospective study collecting data from women and their new born infants who were delivered at and residing in proximity to the study hospitals. Data were collected at delivery and on the second and fifth days following delivery. The protocol was approved by the institute's ethical review board of each hospital as well as the Scientific and Ethical Review Group of the World Health Organization Special Programme of Research, Development and Research Training on Human Reproduction. Data were collected during September 2001 to September 2004.

Eligible criteria included all women delivered in the study hospitals, who could be followed up until the fifth day postpartum. Consecutive eligible delivery cases were identified in the labor rooms and postpartum ward by nursing staff and the subjects invited to participate in the study. In cases of elective (planned) CS, informed consent was obtained prior to delivery or as soon as reasonable after delivery. In cases of emergency CS, admission to the study and informed consent was obtained as soon as reasonable after delivery. In subjects with vaginal delivery, informed consent was obtained and admission to the study performed as soon as reasonable after delivery.

Table 1 General statistics of participating centers

County, city	No. Hospitals involved (specialist maternity hospital)	No. Deliveries/year	No. Neonatal beds	No. Obstetricians
Bangladesh, Dhaka	1 (1)	7 500	20	24
China, Chengdu	3 (1)	2 830	17	33
Indonesia, Medan	3 (3)	7 191	65	50
Indonesia, Padang	1 (0)	2 203	54	15
Mongolia, Ulaanbataar	1 (1)	6 119	107	69
Myanmar, Yangon	1 (1)	8 549	250	78
Nepal, Kathmandu	1 (0)	2 679	10	3
Thailand, Hat Yai	1 (0)	2 684	37	22
Thailand, Khon Kaen	1 (0)	3 500	56	22
Sri Lanka, Colombo	1 (1)	5 375	20	4
Vietnam, Hanoi	1 (1)	9 731	60	80
Vietnam, Ho Chi Minh City	1 (1)	25 009	70	70

Case eligibility was confirmed by the principal investigator(s) in each hospital who also reviewed potential cases on a daily basis. For surveillance of complications, a clinical check list on discharge from hospital was used. By this system, all complications of delivery within 48 h were detected at the hospital. Using a similar check list, all CS patients and sample of patients with vaginal deliveries were followed-up at the hospital or at home within five days. A surveillance system was also set up to identify patients who return to the hospital for any reason within six weeks of delivery. In all centers, causes of death and complication were coded using ICD10 and the operative procedures coded with ICD9-CM. This information was checked by the local principal investigators who had attended a series of investigator meeting prior to and during data collection. With the afore-mentioned check list and criteria, important complications were detected and used in statistical analysis.

The sample size calculation was based on using 95% confidence interval and 80% power. Initial assumptions were an estimated rate of 5% of complications in the vaginal delivery group and 10% among the CS group and the proportion of CS cases to be 20%. With these assumptions, 1092 vaginal deliveries, 273 elective and 273 emergency CS are required. However, as the speed of recruitment varied considerably among countries, it was decided to pool all data from all study centers.

Data coding, monitoring and verification were carried out by the local investigators as soon as the form arrives from the interviewers. Computerization of data was carried out using a specific data entry program compiled from EpiInfo version 6.04.¹⁵ The data were transferred and analyzed using R statistical package.¹⁶ Descriptive statistics were used. Chi-squared test and

Table 2 Sample size by centre and mode of delivery sorted by elective CS rate

	Vagina	Elective CS	Emergency CS	Total
Medan	1 013	283	449	1 745
Padang	1 034	274	394	1 702
Hat Yai	1 044	205	336	1 585
Khon Kaen	1 091	270	285	1 646
Hanoi	1 100	270	257	1 627
Hochiminh City	1 093	273	360	1 726
Chengdu	1 134	298	360	1 792
Dhakha	1 099	272	367	1 738
Colombo	1 080	292	509	1 881
Yangon	1 214	242	373	1 829
Ulaanbataar	1 057	258	447	1 762
Kathmandu	632	125	191	948
Total	12 591	3062	4328	19 981

Fisher's exact test were used to compute the significant difference among groups of deliveries.

Results

Table 1 shows various characteristics of the study hospitals. All were teaching hospitals with residency training programs or the equivalent. The ratio between neonatal beds and number of deliveries increased among non-maternity university hospitals. In total, there were records of 19 981 subjects recruited who gave birth to 19 740 singletons, 109 pairs of twins and 7 sets of triplets. There were 12 591 vaginal deliveries, 3062 elective and 4328 emergency CS.

Table 2 gives the sample size by centre and by mode of delivery sorted by elective CS rate which was lowest (13%) in Hat Yai and highest in Chengdu (16.6%). Emergency CS rate was lowest (15.8%) in Hanoi and highest in Colombo (27%).

The mean age of the patients undergoing elective CS (29.73 years SD 5.6) was significantly higher than that of the emergency CS group (28.17 SD 5.6 years) and that of the vaginal deliveries (26.71 SD 5.5 years). The youngest patients in the total population were aged 13 and 14 years and the oldest 56 years.

The elective CS group were more likely to have had a previous induced abortion, miscarriage or ectopic pregnancy. Of the 540 women with a previous history of stillbirth, 281 (52%) had a vaginal delivery, 24% an elective and 24% an emergency CS. There was a history of a previous CS in 1527 women of whom 159 had a vaginal delivery (10.4%), 911 (59.7%) an elective CS and the remaining 457 (29.9%) had an emergency CS.

There were 20 maternal deaths occurring in four centers. The maternal mortality rate varied by centre, highest in Hat Yai, Thailand (14.9/1000 births), followed by Medan, Indonesia (14.1/1000), Hanoi, Viet Nam (3.9/1000) and Padang, Indonesia (3.7/1000). Emergency CS was most commonly associated with these rates in these centers. Among the three types of CS, deaths were most common in the emergency group.

The list of main causes of death is shown in Table 3. Eclampsia and other pregnancy induced hypertensive conditions were the most common, contributing 10 of these 20 deaths. Other causes included three deaths from serious infections, recorded as septicemia and puerperal sepsis, one due to postpartum hemorrhage and one due to obstructed labor. Major contributing causes included medical and congenital abnormalities of the mother.

Table 3 Causes of maternal death by ICD code

ICD code	Cause	Frequency
O14.1	Severe pre-eclampsia	3
O15.0	Eclampsia in pregnancy	2
O15.2	Eclampsia in labour	2
O15.2	Postpartum eclampsia	2
A41.8/41.9	Septicemia	2
O85.0	Puerperal sepsis	1
O72.1	Postpartum hemorrhage	1
O71.4	Other obstetric trauma	1
O64.2	Obstructed labour due to malposition and malpresentation	1
O10.1	Pre-existing hypertension complicating pregnancy	1
K76.0	Fatty change of liver	1
K72.9	Hepatic failure	1
O88.1	Amniotic fluid embolism	1
Q21.1	Atrial septal defect	1

In Medan there were five deaths attributed to eclampsia, three to postpartum hemorrhage, two cases of septicemia and postpartum sepsis and one case each of hepatic failure, cardiac failure associated with pre-existing hypertension and gestational hypertension. The five deaths in Hat Yai comprised one case each of amniotic fluid embolism, postpartum hemorrhage, intracerebral hemorrhage, cardiac failure with atrial septal defect and disseminated nocardiosis and AIDS. The deaths in Hanoi and Padang were due to face presentation with obstructed labor and eclampsia, respectively.

The emergency CS group had the highest mortality rate (2.9 per 1000 women), which is statistically higher than the rates among the vaginal delivery and the elective CS groups (0.47 and 0.31 per 1000 women, respectively). The difference between the two latter rates is not statistically significant. None of the maternal deaths was associated with multiple pregnancies.

Maternal complications

Similar to that seen with the maternal mortality rate, there is a consistent ascending order of complications of delivery from vaginal delivery to elective CS and highest at emergency CS as shown in Table 4. These complications include postpartum fever, minor wound infection, peritonitis, urinary problems, hemorrhage needing blood transfusion, hysterectomy, internal iliac artery ligation and anesthetic complications.

Compared to elective CS, emergency CS had a higher rate of major wound problems needing extra hospital stay ($P=0.007$) and secondary operation ($P<0.001$).

Both types of cesarean section had higher rates of postpartum pyrexia than vaginal delivery. Overall, the highest percentages of women with postpartum pyrexia were seen in Kathmandu (10.5% of women), Ho Chi Minh City (8.0%), Yangon (6.4%) and Medan (6.1%). Postpartum urinary tract infections or symptoms were more common in the CS groups and highest in Kathmandu (38.4% of women), Khon Kaen (28.3%) and Dakha (24.1%). Blood transfusion was more commonly reported in the emergency CS group than the elective CS women. In Medan, 7.8% of the women undergoing elective CS and 24.5% of the emergency CS group were transfused and in Padang the corresponding figures were 2.2 and 13.3%.

Internal iliac artery ligation was exclusively performed in both types of CS with more or less equal rates.

Table 4 Maternal complication rates (per 1000 deliveries with 95% CI) among vaginal delivery, elective and emergency CS

	Vaginal delivery	Elective CS	Emergency CS	P value*
Maternal death	0.47 (0.17, 1.03)†	0.31 (0.01, 1.73)†	2.87 (1.53, 4.91)	<0.001
Fever	5.7 (4.5, 7.2)	16.7 (12.4, 21.8)†	18 (14.3, 22.4)†	<0.001
Minor wound infection	21.9 (19.4, 24.6)	84.9 (75.3, 95.4)	116 (106.6, 125.9)	<0.001
Peritonitis	0.2 (0, 0.6)	2.6 (1.1, 5.1)†	4.6 (2.8, 7.1)†	<0.001
Urinary problem	26.1 (23.3, 29)	54.9 (47.1, 63.5)	71.4 (63.9, 79.5)	<0.001
Hemorrhage	13.7 (11.7, 15.8)	21.2 (16.4, 27)	63.5 (56.4, 71.2)	<0.001
Hysterectomy	1.7 (1.1, 2.6)†	3.3 (1.6, 6)†‡	7.2 (4.9, 10.2)‡	<0.001
Internal iliac artery ligation	0 (0, 0.3)	2.9 (1.3, 5.6)†	2.5 (1.3, 4.5)†	<0.001
Anesthetic complication	0 (0, 0.3)	22.5 (17.6, 28.4)†	25.9 (21.4, 31.1)†	<0.001
Major wound infection	3.7 (2.7, 5)†	2 (0.7, 4.3)†	6.5 (4.3, 9.3)	0.007
Second operation	37.7 (34.5, 41.2)	1.3 (0.4, 3.3)†	1.6 (0.7, 3.3)†	<0.001
Endometritis	0.6 (0.2, 1.1)	0.3 (0, 1.8)	1.4 (0.5, 3)	0.143

*Chi-squared test or Fisher's exact test (when >20% of expected value were <5). †,‡Different groups having the same superscript are not significantly different from each other if the overall P value is <0.05.

Table 5 Neonatal complication rates (per 1000 deliveries with 95% CI) among vaginal delivery, elective and emergency CS

	Vaginal	Elective CS	Emergency CS	Fisher's exact test P value
Dead	7 (5.6, 8.6)	2.2 (0.9, 4.6)	12.4 (9.3, 16.2)	<0.001
Moderate asphyxia	10.9 (9.2, 12.9)	17.9 (13.5, 23.1)†	25.3 (20.8, 30.5)†	<0.001
Severe asphyxia	4.3 (3.2, 5.6)	1.3 (0.3, 3.3)	8 (5.5, 11.1)	<0.001
Jaundice needing therapy	19 (16.7, 21.6)†	22 (17.2, 27.8)†	30.6 (25.6, 36.2)	<0.001
Anemia needing transfusion	1 (0.5, 1.7)	1 (0.2, 2.8)	1.4 (0.5, 3.1)	0.663
Fracture	0.5 (0.2, 1)	0.6 (0.1, 2.3)	0.2 (0, 1.3)	0.71
Palsy	1.3 (0.7, 2.1)	0.3 (0, 1.8)	0.9 (0.3, 2.4)	0.356
Internal organ damage	0.2 (0, 0.6)	1.3 (0.3, 3.3)†	2.1 (1, 4)†	<0.001
Intracranial hemorrhage	1 (0.5, 1.7)	0 (0, 1.2)	0.7 (0.1, 2.1)	0.25

†Different groups having the same superscript are not significantly different from each other if the overall P value is <0.05.

Major wound infections were most commonly seen in the emergency CS group with the highest rates seen in Ho Chi Minh City (6.6% of women), Yangon (5.0%) and Medan (2.6%). On the other hand, second operations were most commonly needed among vaginal delivery group. Endometritis rates were however, not significantly different among different modes of delivery ($P = 0.142$).

Neonatal deaths and complications

There were 163 stillbirths: 149 were singleton, 6 were first and 8 were second twins. The stillbirth rates (SBR) per 1000 births varied from 26.1 in Padang, 18.7 in Medan, 11.5 in Kathmandu, 9.7 in Yangon, 9.5 in Dakha, 6.4 in Columbo, 4.2 in Hanoi, 3.9 in Ulanbatar, 3.1 in Hat Yai, 1.6 in Khon Kaen, 1.1 in Chengdu, and 0 in Hochimin City. This rate was highest in the emergency CS group (12.6%) followed by the vaginal delivery group (7.7%) and lowest in the elective CS group (2.1%) (Chi-squared test, $P < 0.001$).

The number of early neonatal deaths (NND) was 147 (7.4 per 1000 live births), 131 singletons and 7 first and 9 second twins. In all centers except Khon Kaen, Hanoi, Chengdu and Ulanbatar, the rates were highest in emergency CS group. Centers with high neonatal death rates after adjusted for distribution of mode of delivery were Padang and Medan with the rates of 15.0 and 11.8 per 1000 live births, respectively. Centers with early NND rate below 2 per 1000 live birth were Hat Yai, Khon Kaen and Hanoi. Other centers had this rate between these to extreme groups. The different rates among centers were statistically significant ($P < 0.001$).

From the first row of Table 5, it can be seen that death and complication rates in the fetal and neonatal cohort were different from maternal complication rates. Elective CS has lowest early neonatal mortality rate (2.2/1000 births), significantly lower than those in the vaginal delivery (7.0) and the emergency CS group (12.4). Having vaginal delivery group as reference and with adjustment for centre, odds ratio was

0.31 (95% CI = 0.14, 0.67) for elective CS and 1.68 (95% CI = 1.19, 2.37) for emergency CS.

Of important neonatal complications, significantly lowest rates observed in the vaginal group were moderate asphyxia (Apgar score at 5 min of lower than 7 and greater than 4), jaundice needing therapy and internal organ damage. Neonatal complications with the lowest rate in the elective CS was severe asphyxia (Apgar score at 5 min of 4 or lower). The rates for anemia needing transfusion, fracture, palsy and intracranial hemorrhage were not significantly different among groups.

Discussion

This study confirms that in a large number of teaching hospitals in South and East Asia, the rate of various maternal complications generally increases from vaginal delivery to elective and emergency cesarean deliveries. On the fetal side, elective CS demonstrated its benefits by having the lowest early neonatal complication rates followed by vaginal and emergency cesarean delivery.

The findings of high rates of complications have been reported from previous studies, principally in developed countries³⁻⁹ and country and region-specific rates are described by Bertran *et al.*⁷ Most of them have been retrospective medical record reviews where the assessment was confined to time of discharge from the hospital and the definitions of specific types of complication varied from one study to another. Moreover, very few had a comparison group of vaginal deliveries.

However, direct comparisons between CS rates found in our study and those estimated from Demographic and Health Surveys (DHS) are not particularly useful as the DHS used retrospective questionnaires and the study data in this paper are derived from a prospective study in a tertiary care teaching hospital environment.

Eclampsia was the most common cause of maternal death in this study with six cases and a further three cases of maternal death associated with severe pre-eclampsia, suggesting inadequate management of pregnancy-induced hypertension, compared to other classic causes of death such as hemorrhage and infection. The study hospitals were mainly referral centers often with seriously complicated cases. In the community, the range of causes would probably be different.

The overall still birth rate in this study of 7.9/1000 births is much lower than that quoted for South-central Asia (33/1000 births) and 15/1000 births for South-

eastern Asia by WHO.¹⁷ With the exception of the two Indonesian centers in our study, the SBR results are also lower than those cited by WHO for individual Asian countries. The WHO data were compiled from DHS and national surveys and were not confined to tertiary care facilities as in our study and therefore are not strictly comparable.

The relationship between mode of delivery and the outcomes however, should be interpreted with caution. Selection of the mode was not randomly assigned by indication. Emergency cesarean delivery is generally considered as a life saving obstetric procedure and patients who had indications for this procedure would have already been at risk compared to elective cesarean and vaginal delivery and thus prone to higher complication rate.

Elective cesarean delivery is usually performed under controlled conditions. Although indications for elective cesarean delivery may predispose the patients to subsequent complications, with better prepared conditions, the level of predisposition would be lower than in the emergency situation.

From our data, cesarean deliveries, regardless of whether elective or emergency, introduce excess risk of various types such as anesthetic complications, major wound infections and hemorrhage. On one hand, our data suggest that various procedures in cesarean deliveries did exert significant additional risk to the women. This excess risk was not balanced by the reduction in the number of less serious complication specific to vaginal deliveries such as perineal wound infections and secondary operation. On the other hand, the relationship between emergency CS and the complications could be confounded by indication. In other words, a higher risk woman who tended to have bad delivery outcome might be more likely to undergo emergency CS. Moreover, in certain cases, the relationship could even be reverse causal. For example, excessive bleeding might dictate the need for emergency CS. Therefore, the data must be interpreted with caution.

The overall findings on the fetal and neonatal aspects were different from the maternal side in that there were relatively low fetal complication rates observed in the elective cesarean delivery group. Since this procedure is usually indicated in certain high risk pregnancies, had elective section not been carried out, more complications would be expected among the vaginal and emergency cesarean delivery groups.

In conclusion, cesarean deliveries can increase maternal complications significantly. It should be restricted to the high risk patients. Elective section,

when properly chosen, can reduce maternal complication from emergency section and save the fetus and neonate from complications.

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Screening and treating asymptomatic bacteriuria in pregnancy

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Purpose of review

Asymptomatic bacteriuria (ASB) in pregnancy, if left undiagnosed and appropriately treated can lead to acute pyelonephritis in mothers and low birth weight in infants. Urine culture is the gold standard for diagnosing ASB. Unfortunately, urine culture is limitedly available. The present review aims at evaluating performance of various screening tests and effectiveness of antibiotic regimens for ASB.

Recent findings

Positive dipstick test is very likely to have a definitive diagnosis of ASB, whereas a negative result effectively rules out ASB. Available evidences regarding the performance of urine dipstick are still conflicting, it is currently not appropriate to recommend urine dipstick for screening ASB in pregnancy. Choice of antibiotics should be guided by antimicrobial susceptibility testing whenever possible. Nitrofurantoin seems to be antibiotic of choice for ASB in pregnancy. Seven-day regimen of antibiotics gives a better microbiological cure rate but no difference in important clinical outcomes compared with 1-day regimen.

Summary

Dipstick culture is a promising screening test for ASB. Pregnant women with ASB should be treated with 7-day regimen of antibiotics, although 1-day regimen might be appropriate in some settings. More research is needed for identifying appropriate screening tests for ASB.

Keywords

asymptomatic bacteriuria, pregnancy, screening, treatment

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Introduction

Asymptomatic bacteriuria (ASB) is generally defined as the presence of significant bacteriuria without symptoms. The US Preventive Services Task Force (USPSTF) recommends screening for ASB with urine culture in pregnant women at 12–16 weeks gestation or at the first prenatal visit, if later [1]. Unfortunately, urine culture is not widely available. Some more simple methods have been used for screening ASB [2]. A *Cochrane* review shows that antibiotic treatment for ASB in pregnancy is effective in reducing the risk of pyelonephritis and low birth weight [3]. The present review aims at evaluating the screening and treatment of ASB in pregnancy.

Definition of asymptomatic bacteriuria

ASB is defined as the presence of significant bacteriuria without the symptoms of an acute urinary tract infection (UTI). Significant bacteriuria is the presence of two consecutive clear-voided urine specimens both yielding positive cultures of the same uropathogen more than 10^5 colony-forming units (cfu)/ml of urine [4].

Epidemiology of asymptomatic bacteriuria in pregnancy

Recent studies reported the prevalence of ASB in pregnancy to be 2.5–15% [2*,5,6*]. *Escherichia coli* was the most common potentially pathogenic bacteria detected [2*,5,6*]. Risk factors of ASB in pregnancy include history of previous UTI, low socioeconomic status [7] and lower education [8]. A *Cochrane* review showed that antibiotic treatment was effective in clearing ASB [risk ratio (RR) 0.25, 95% confidence interval (CI) 0.14–0.48] and reducing incidence of pyelonephritis (RR 0.23, 95% CI 0.13–0.41). Antibiotic treatment also reduced the incidence of low birth weight (RR 0.66, 95% CI 0.49–0.89) but a difference in preterm delivery was not seen [9].

Diagnosis of asymptomatic bacteriuria in pregnancy

An important issue in the diagnosis of ASB is differentiating contamination from significant bacteriuria.

Urine culture

The original criterion for clinically significant ASB, positive cultures of the same uropathogen more than

10^5 cfu/ml of urine on two consecutive clean-catch specimens, has a 95% probability that the pregnant woman has true bacteriuria. The detection of more than 10^5 cfu/ml in single-voided midstream urine is accepted as a more practical and adequate option, although there is only an 80% probability the woman has true bacteriuria [10]. Urine culture is still the gold standard and the test of choice for detecting ASB. It is time-consuming, 24–48 h to obtain result, and also requires a microbiology laboratory with qualified staff. It is therefore not possible for urine culture to be a universal screening test for all levels of healthcare centers, especially in developing countries where only limited laboratory facilities and experienced staff are available [11].

Many screening tests for ASB are available. The tests include urine Gram stain, microscopic urinalysis, urine dipsticks, dipslide urine cultures, bioluminescence assay, etc. An ideal screening test should be simple, rapid, sensitive, specific and not too expensive so that it can be implemented in all settings. The decision about the test to screen ASB in pregnancy is a balance between the performance of the test and cost of screening.

Dipslide culture

The dipslide, a rapid screening test, is simpler to perform and can be applied as an office screening test. The device consists of a plastic paddle coated on both sides with agar media, one side for the detection of Gram-negative organisms (coated with MacConkey agar) and the other side supports the growth of all organisms (coated with cysteine-lactose-electrolyte-deficient agar). The dipslide is inoculated by dipping the agar-coated slides into the urine specimen, enough to wet both agar surfaces and incubated for 18–24 h at 35°C. The colony counts of the Uricult (Lifesign LLC, Somerset, New Jersey, USA) are determined using a color chart. This method cannot identify the specific species of bacteria isolated. Once significant growth is detected, standard urine cultures have to be done for species identification [12]. The test results can be read directly by physicians or paramedical personnel without waiting for laboratory responses. There is also the potential advantage of directly culturing a freshly voided urine sample, eliminating the risk of potential overgrowth of commensal flora during transport to the laboratory [13]. In this respect, it is well known that leaving urine specimens at room temperature for a prolonged period of time may modify the final counts of microorganisms. A proven accurate dipslide test would be of greater value where delays between the clinics and the laboratory are either unavoidable, unpredictable, or both, and where facilities for refrigeration are unavailable [14]. In addition, it could contribute to reducing the costs of testing women for ASB and would be very suitable for settings in which healthcare resources in terms of laboratory and trained personnel are limited [13].

There are studies evaluating the diagnostic performance of dipslide test as a more feasible alternative test to urine culture [2*, 15–17]. A recent published study of diagnostic tests confirmed the ability of dipslide tests in screening ASB during pregnancy. The prevalence of ASB was 15%, and *E. coli* was the most prevalent organism. The authors found that the dipslide had high accuracy; the likelihood ratio for a positive dipslide test was 225 (95% CI 113–449), increasing the probability of ASB to 98%. Conversely, the likelihood ratio for a negative dipslide test was 0.02 (95% CI 0.01–0.05), reducing the probability of bacteriuria to less than 1%. In addition the tests had advantages regarding their use. They concluded that dipslide should be considered as valid alternative to the standard culture. The conclusions also suggested that a pregnant woman with a positive dipslide test is very likely to have a definitive diagnosis of ASB, whereas a negative result effectively rules out the presence of bacteriuria [2*]. However, this was an ancillary study within a trial comparing single-day with 7-day therapy in treating ASB [6*]. The authors suggest having further research in more pragmatic conditions before recommending the dipslide as an office-screening test [2*].

Urine dipstick

Urine dipstick tests with individual and combination components mainly of leukocyte esterase and nitrite are the other potential tests for rapid diagnosis of ASB during pregnancy. The tests are easy to perform and do not need a laboratory or trained laboratory personnel. The results of the dipstick test are instant whereas the standard culture takes 24–48 h for definitive diagnosis. There are reports evaluating the performance of urine dipstick for rapid diagnosis of ASB [18–23]. The results of these primary studies are conflicting.

In Garingalo-Molina's systematic review [24], five studies using urine dipsticks showed generally low sensitivity, variable specificity, positive predictive and negative predictive values (NPVs). None recommended the tests as sufficient screening method. However, a more recent meta-analysis of the accuracy of the urine dipstick to rule out a urine infection also included studies of pregnant women [25]. Ten studies in pregnancy with both symptomatic bacteriuria and ASB were included in the subgroup analyses of diagnostic performance of nitrites on urine dipsticks. The accuracy of nitrites was concluded high in pregnant women with a diagnostic odds ratio (95% CI) of 165 (73–372) and that a negative test for both leukocyte esterase and nitrites could rule out UTIs in asymptomatic pregnant women. Positive results, however, need confirmation. If positive results are proven, it will be useful in follow-up of patients after treatment of UTI. This is useful in poor resource settings especially in the third world where there is lack of trained personnel and equipment for urine culture [25]. As available

evidences are still conflicting, it is not appropriate to recommend urine dipstick as a screening test for ASB in pregnancy.

Other tests

Performance of the other rapid screening tests, that is, urine Gram stain, microscopic urinalysis, bioluminescence assays, etc. for detecting ASB in pregnant women were also reported in various settings [26–30]. A report from India evaluating Gram's staining of uncentrifuged urine, pus cell count, compared against urine culture. Gram's stain of the uncentrifuged urine had a sensitivity and NPV of 85.1% and 98.8%, respectively. Pus cell count was the least sensitive [26]. Performance of enhanced urinalysis (uncentrifuged urine white blood cell count/ml plus Gram stain) in detecting ASB in obstetric patients was evaluated by a study from Turkey. Clean-catch midstream urine specimens were collected from 250 consecutive asymptomatic pregnant women, a prevalence of ASB was 4%. The sensitivity and specificity of enhanced urinalysis were found to be 50.0 and 96.7%, respectively [31]. Simple urinalysis and urine culture were performed on 774 pregnant women in Thailand. Simple urinalysis had a sensitivity of 18.4, a specificity of 97.2%, 45.7% positive predictive value, 90.4% NPV and 88.4% accuracy in detecting ASB. The authors concluded that because of its low sensitivity and the possible consequences of ASB, simple urinalysis should not be used as a screening test for ASB in pregnancy [32]. An evaluation of bioluminescence assay compared with standard culture as a screening test for the detection of ASB in pregnancy was conducted in 1000 pregnant women in Austria. Bioluminescence screening had 93% sensitivity, 78% specificity and 99% predictive accuracy for negative results. The authors concluded that bioluminescence assay was an effective, time-saving and labor-saving but questionably cost-effective method for the detection of bacteriuria in pregnancy [30]. Evidences from these reports do not support their uses in screening ASB in pregnancy. However, some of these tests are still widely used because they are easy to perform and produce results rapidly.

Treatment of asymptomatic bacteriuria in pregnancy

Many antenatal guidelines include routine screening and treatment for ASB in pregnancy as recommended by American College of Obstetrics and Gynecology (ACOG), Infectious Diseases Society of America (IDSA) and USPSTF [33–35].

Rationale for treatment of asymptomatic bacteriuria in pregnancy

A recent *Cochrane* review showed that antibiotic treatment was effective in clearing ASB (RR 0.25, 95% CI 0.14–0.48) and reducing the incidence of pyelonephritis (RR 0.23, 95% CI 0.13–0.41). Antibiotic treatment also reduced the incidence of low birth weight (RR 0.66, 95% CI 0.49–0.89) but a reduction in preterm delivery was not observed (RR 0.37; 95% CI 0.10–1.36) [9].

Selection of antibiotics

The most common pathogen in ASB in pregnant women is *E. coli*. Other common uropathogens include *Klebsiella pneumoniae*, *Proteus mirabilis*, *Streptococcus* group B, *Enterococcus* and *Staphylococcus saprophyticus* [2*,6*]. Various antibiotics are available for the treatment of ASB in pregnancy as summarized in Table 1. Commonly used antibiotics are ampicillin (pivampicillin), amoxicillin, trimethoprim, sulfonamide and nitrofurantoin [36]. Antibiotics chosen for the treatment of ASB should have high efficacy, low resistance rate and good maternal and fetal outcomes. As *E. coli* is the most common pathogen in ASB in pregnancy, empirical antimicrobial agent for initial treatment should be considered. Unfortunately, up to 40% of isolated *E. coli* are resistant to ampicillin and sulfonamides [37]. Ampicillin and sulfonamides are therefore not recommended for empirical treatment in areas where *E. coli* resistance is common. Nitrofurantoin has a relatively low level of resistance among community-acquired uropathogens due to its multiple mechanisms of action. However, nitrofurantoin may cause hemolysis in glucose-6-phosphate dehydrogenase deficient patients and should be used with caution especially in high

Table 1 Common antibiotics for asymptomatic bacteriuria in pregnancy

Type of antibiotics	Advantages and disadvantages
1. Amoxicillin	No evidence of teratogenic effect High resistance rates
2. Cephalosporin	No evidence of teratogenic effect Not active against <i>Enterococcus</i> spp.
3. Nitrofurantoin	No evidence of teratogenic effect, few or no changes in bacterial resistance rates, covers <i>E. coli</i> and <i>Enterococcus faecalis</i> but not active against <i>Proteus</i> and <i>Pseudomonas</i> spp., may cause hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency
4. Trimethoprim-sulfamethoxazole	High resistance rates, trimethoprim is associated with neural tube and other birth defects when using in the first trimester, sulfonamides should be avoided after 32 weeks' gestation as it could cause severe jaundice leading to kernicterus, acute hemolytic anemia in newborns with G6PD deficiency
5. Fosfomycin	Single dose therapy is as effective as multiple doses of other antibiotics, low incidence of resistance <i>E. coli</i> , does not cover <i>S. saprophyticus</i> , there is limited experience for using in pregnancy

prevalence areas [38]. Cephalosporin is another alternative if there is bacterial resistance to first line drugs. Cephalexin is an oral cephalosporin that is most widely used in pregnancy [39]. However, cephalosporin is not effective for *Enterococcus* spp. [40]. Fosfomycin, a derivative of phosphonic acid, can also be used to treat lower UTI. A randomized trial comparing single dose of fosfomycin with 7–10 day course of nitrofurantoin, norfloxacin, co-trimoxazole found no differences of effectiveness in treating uncomplicated lower UTI [41]. However, caution is advocated as there is limited experience for using in pregnancy [36]. The choice of antibiotics should be guided by antimicrobial susceptibility testing whenever possible, but this decision is becoming more difficult because of increasing rates of antimicrobial resistance to commonly prescribed antibiotics.

Duration of treatment

A *Cochrane* systematic review of duration of treatment for ASB during pregnancy that was updated in 2006 found that the 4–7 day regimen is not more effective than 1-day or single dose regimen in term of bacteriological cure rate. A recent WHO multicenter randomized noninferiority trial reported that 1-day regimen of nitrofurantoin is significantly less effective than a 7-day regimen in treating women with ASB [6^{*}]. The bacteriological cure rates for 7-day and 1-day regimen were 86.2 and 75.7% respectively. The cure rate difference was 10.5% (95% CI 16.1, 4.9%). Mean birth weight and mean gestational age at delivery were statistically significantly lower in the 1-day regimen group (3159g compared with 3059g; mean difference 100; 95% CI 181, 18 and 38.7 weeks compared with 38.4 weeks; mean difference 0.3; 95% CI 0.7 and 0.05, respectively). However, there is no difference between 7-day and 1-day regimen for the outcomes of symptomatic UTI, preterm delivery, adverse effects and low birth weight. This marginal but statistically significant improvement in bacteriological cure with the 7-day regimen was debated to be balanced against the advantages of the 1-day regimen. As the 1-day regimen was not associated with increased adverse perinatal outcomes, it may be considered to be as effective as the 7-day regimen. In situations when compliance and cost are problematic, a 1-day antibiotic treatment could be beneficial, although a 7-day regimen is preferable if feasible [42]. However, in developing countries where urine culture is usually very limited and follow-up urine culture after treatment until negative is not practical we may need the most effective regimen with acceptable adverse effects at affordable cost of 7-day regimen of nitrofurantoin [43].

Conclusion

ASB is quite common in pregnancy. All pregnant women should be routinely screened and appropriately treated for ASB. Urine culture is currently the gold standard for

detecting ASB during pregnancy. Dipslide culture is a promising alternative as a screening test for ASB. Pregnant women with ASB should be treated with 7-day regimen of antibiotics wherever possible, although 1-day regimen might be appropriate in some settings. More research is needed for identifying appropriate screening tests for ASB.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 186).

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Misoprostol as an adjunct to standard uterotonics for treatment of post-partum haemorrhage: a multicentre, double-blind randomised trial

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Summary

Background Post-partum haemorrhage is a leading cause of global maternal morbidity and mortality. Misoprostol, a prostaglandin analogue with uterotonic activity, is an attractive option for treatment because it is stable, active orally, and inexpensive. We aimed to assess the effectiveness of misoprostol as an adjunct to standard uterotonics compared with standard uterotonics alone for treatment of post-partum haemorrhage.

Methods Women delivering vaginally who had clinically diagnosed post-partum haemorrhage due to uterine atony were enrolled from participating hospitals in Argentina, Egypt, South Africa, Thailand, and Vietnam between July, 2005, and August, 2008. Computer-generated randomisation was used to assign women to receive 600 µg misoprostol or matching placebo sublingually; both groups were also given routine injectable uterotonics. Allocation was concealed by distribution of sealed and sequentially numbered treatment packs in the order that women were enrolled. Providers and women were masked to treatment assignment. The primary outcome was blood loss of 500 mL or more within 60 min after randomisation. Analysis was by intention to treat. This study is registered, number ISRCTN34455240.

Findings 1422 women were assigned to receive misoprostol (n=705) or placebo (n=717). The proportion of women with blood loss of 500 mL or more within 60 min was similar between the misoprostol group (100 [14%]) and the placebo group (100 [14%]; relative risk 1.02, 95% CI 0.79–1.32). In the first 60 min, an increased proportion of women on misoprostol versus placebo, had shivering (455/704 [65%] vs 230/717 [32%]; 2.01, 1.79–2.27) and body temperature of 38°C or higher (303/704 [43%] vs 107/717 [15%]; 2.88, 2.37–2.50).

Interpretation Findings from this study do not support clinical use of 600 µg sublingual misoprostol in addition to standard injectable uterotonics for treatment of post-partum haemorrhage.

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Introduction

Haemorrhage is the leading cause of maternal mortality in low-resource settings:¹ an estimated 125 000 deaths are due to post-partum haemorrhage every year.² Maternal death from haemorrhage is rare in high-resource settings, suggesting that medical interventions for haemorrhage contribute substantially to survival. Conventional treatment of post-partum haemorrhage relies heavily on hospital-based interventions. However, post-partum haemorrhage is largely unpredictable,³ and can lead to death within hours. Simple treatment methods are needed for implementation at all levels of care.

Misoprostol is a prostaglandin E1 analogue that is widely marketed in tablet form, and is registered for use in the prevention and treatment of peptic ulcer disease. It is thermostable, can be taken orally, and is fairly inexpensive. Although misoprostol is less effective than oxytocin for prevention of post-partum haemorrhage,⁴ it has been promoted widely for the ease with which the drug can be taken,⁵ and the positive results from a trial of misoprostol administration by rural birth attendants in India.⁶ Concerns about misuse⁷ and side-effects⁸ have

emerged, and misoprostol use for labour induction seems to increase post-partum blood loss.⁹

Clinical use of misoprostol for post-partum haemorrhage is based on weak evidence.^{10,11} At the start of our study, three randomised trials of misoprostol for treatment of post-partum haemorrhage had been published.^{12–14} Lokugamage and colleagues¹² reported that 800 µg rectal misoprostol stopped post-partum haemorrhage significantly more effectively than did combined intramuscular syntometrine and intravenous syntocinon. However, in that trial treatment allocation was unblinded and the outcome was subjective assessment of clinical response, so investigator bias could have favoured the misoprostol group. Hofmeyr¹³ and Walraven¹⁴ and their colleagues did double-blind trials and showed reduced blood loss with misoprostol compared with placebo, both in combination with standard uterotonics, but the differences were not significant. In a meta-analysis of the results of these trials, misoprostol significantly reduced the primary outcome of additional blood loss of 500 mL or more (relative risk 0.57, 95% CI 0.34–0.96).¹⁵ However, in a systematic review, Mousa and Alfirevic¹⁶ concluded that evidence for any advantage from

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addition of misoprostol to standard uterotonic treatment was insufficient, and called for more safety data on misoprostol as adjunctive treatment for post-partum haemorrhage.¹⁶ The main side-effects of misoprostol are shivering and pyrexia, which are dose-dependent.^{11,17}

We aimed to establish whether further blood loss could be reduced with the addition of 600 µg misoprostol sublingually to standard uterotonic treatment (mostly oxytocin) in women with post-partum haemorrhage that was suspected to be caused by uterine atony in vaginal delivery. Findings from pharmacokinetic data show that sublingual administration results in the most rapid absorption, and the highest serum concentrations and bioavailability.^{18,19} Reduced blood loss with this simple, inexpensive adjunctive treatment for post-partum haemorrhage could have major public health implications. Conversely, demonstration of lack of efficacy would provide evidence to help avoid further use of an ineffective and potentially harmful drug.

Methods

Participants

All women delivering vaginally were eligible to participate in the study if they had clinically diagnosed post-partum haemorrhage that was suspected to be due to uterine atony, and they needed additional uterotonics. Participants were enrolled from hospitals in Argentina, Egypt, South Africa, Thailand, and Vietnam between July, 2005, and August, 2008. Women were not eligible for the trial if: delivery was by caesarean section; misoprostol could not be given sublingually; any severe allergic or bleeding disorders (eg, haemophilia) were recorded; temperature was higher than 38.5°C; the delivery was defined as a miscarriage according to local gestational age limits; or the placenta was not delivered.

Women were provided with information about the trial during antenatal care. At admission for delivery, women were approached to participate in the trial and invited to give informed consent; all women provided written consent. The trial was approved by the ethics committees of the participating centres and by the Scientific and Ethical Review Group for the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction. The findings are reported in accordance with the revised CONSORT guidelines.²⁰

Randomisation and masking

A computer-generated randomisation sequence was derived centrally by Gynuity Health Projects (New York, NY, USA), and was stratified by country. Within the strata women were individually allocated by block randomisation (varying blocks of six and eight) to receive 600 µg misoprostol sublingually (three tablets of 200 µg; GyMiso, HRA Pharma, Paris, France) or matching placebo; both groups received standard uterotonics. The standard uteronic was in most cases 10 IU oxytocin given

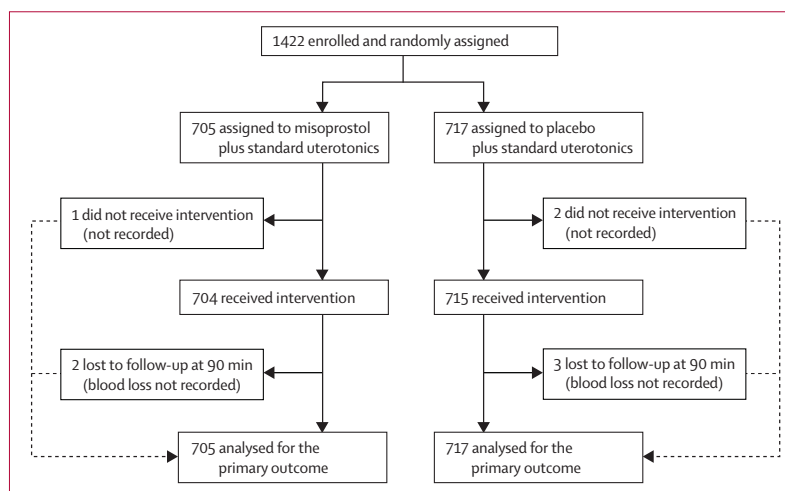


Figure 1: Trial profile

	Misoprostol (n=705)	Placebo (n=717)
Age (years)	26 (5.6)	26 (6.0)
Nulliparous	287 (41%)	290 (40%)
Type of uterotonic given during active management of third stage of labour		
Oxytocin	688 (98%)	701 (98%)
Ergometrine	44 (6%)	49 (7%)
Prostaglandins	8 (1%)	6 (1%)
Any uterotonic taken before study drug	645 (91%)	647 (90%)
Birthweight of neonate (g)	3148 (589)	3164 (557)

Data are mean (SD) or number (%).

Table 1: Baseline characteristics of participants

intramuscularly or by slow intravenous injection. The use of uterine massage was not consistent. The randomisation code was not shown to any participating trial centre or member of the study team until the trial was closed.

Treatment boxes were identical in appearance for both groups, and placebo tablets were identical in shape, colour, weight, feel, and taste to misoprostol tablets. To conceal allocation, treatment boxes were sealed and numbered sequentially according to the randomisation sequence, and distributed in the order that women were judged to be eligible and were enrolled in the study. After diagnosis of post-partum haemorrhage, standard uterotonics were given immediately as per standard practice at participating hospitals. Participants were then randomly allocated to treatment by the health provider, and received the study drug as soon as possible after standard uterotonics. Both providers and participants were masked to treatment allocation.

Procedures

The primary outcome was measured blood loss of 500 mL or more within 60 min after randomisation. Secondary outcomes were: need for blood transfusion; haemoglobin concentration of less than 80 g/L within 24 h post partum

	Misoprostol (n=705)	Placebo (n=717)	Relative risk (95% CI)
Primary outcome			
Blood loss of ≥ 500 mL within 60 min after randomisation	100 (14%)	100 (14%)	1.02 (0.79 to 1.32)
Secondary outcomes			
Blood transfusion after randomisation	103 (15%)	117 (16%)	0.89 (0.70 to 1.14)
Haemoglobin concentration of < 80 g/L within 24 h post partum or need for blood transfusion*	121 (18%)	139 (20%)	0.89 (0.72 to 1.11)
Blood loss after randomisation			
Within 60 min (mL)	200 (100–306)	200 (100–340)	0 (0 to 0)†
≥ 1000 mL	9 (1%)	9 (1%)	1.02 (0.41 to 2.55)
Within 90 min (mL)‡	250 (120–440)	250 (120–450)	0 (–40 to 20)†
≥ 500 mL	149 (21%)	162 (23%)	0.93 (0.77 to 1.14)
≥ 1000 mL	17 (2%)	22 (3%)	0.78 (0.42 to 1.47)
Any uterotonic after randomisation	188 (27%)	203 (28%)	0.94 (0.79 to 1.11)
Maternal death	2 ($< 1\%$)	0	NA
Severe morbidity§	8 (1%)	10 (1%)	0.81 (0.32 to 2.00)

Data are number (%) or median (IQR), unless otherwise indicated. NA=not applicable. *Data were recorded for 691 patients receiving misoprostol and 710 patients receiving placebo; outcomes could not be measured in remaining patients. †These data are median difference (95% CI). ‡Data were recorded for 703 patients receiving misoprostol and 714 patients receiving placebo; outcomes could not be measured in remaining patients. §Defined as hysterectomy or admission to a maternal intensive care unit.

Table 2: Primary and secondary outcomes

or need for blood transfusion; median blood loss at 60 min and 90 min after randomisation; blood loss of 500 mL or more within 90 min after randomisation; blood loss of 1000 mL or more within 60 min and 90 min after randomisation; need for any additional uterotonic; maternal death; severe morbidity (hysterectomy or admission to a maternal intensive care unit); side-effects (shivering, pyrexia, diarrhoea, vomiting, or nausea) within 60 min and 90 min after randomisation; and need for any other interventions. Unless otherwise specified, all secondary outcomes were recorded from randomisation up until discharge. Providers assessed side-effects by direct observation or questioning of participants, and every woman with a side-effect was asked to classify the side-effect as mild, moderate, or severe. Any side-effect needing treatment was recorded as severe. Body temperature was assessed with standard thermometers that were routinely used in every hospital.

The trial adhered to the methods used for blood loss measurement in the WHO trial of misoprostol for the prevention of post-partum haemorrhage.⁴ Blood collection started immediately after the study drug was given. A fresh, non-absorbent sheet was placed under the buttocks of the woman. A low-profile plastic fracture bedpan was positioned below the woman's perineum to collect all subsequent blood lost for 90 min. The blood in the bedpan plus any spilled blood from the non-absorbent sheet or blood-soaked gauze swabs, or both, was transferred to a jar and the volume was measured. At the centre in Egypt, blood was collected into a calibrated plastic sheet that was placed below the woman immediately after she took the

study drug, and the volume was measured accordingly. Measures of blood loss were recorded at 60 min and 90 min after randomisation. If bleeding did not stop, providers continued to provide standard care for post-partum haemorrhage according to local protocol. Thus the only addition to routine care was use of the study drug.

Baseline characteristics, blood loss at 60 min and 90 min after randomisation, side-effects and all other interventions were obtained and recorded on paper forms by trained study staff at the time of the delivery; data were reviewed by the principal investigator at each hospital. All data entry forms were stored at the participating hospital. Data were entered locally into a centralised online database developed by the Geneva Foundation for Medical Education and Research, Switzerland. All data were available for viewing by designated study monitors throughout the trial. Regular monitoring continued throughout the trial period to ensure protocol adherence and reliable data recording and data entry.

The data safety and monitoring board convened twice to review the data. After 400 women had been recruited, the first meeting took place to review the rate of side-effects with 600 µg misoprostol, and to confirm that the trial had an adequate sample size. After 700 women had been recruited, the second meeting took place to assess treatment effectiveness. The trial investigators were advised to continue with recruitment after both interim analyses.

Statistical analysis

On the basis of a systematic review of previous trials,¹¹ we estimated that additional blood loss of 500 mL or more would occur in about 16% of women on placebo. Therefore, 691 women per group would be needed to detect a reduction to 10% in women receiving misoprostol (relative risk reduction of 37%) at a 5% significance level (two-sided test) with 90% power, so the trial size was set at 1400 women.

All analyses were by intention to treat. Comparisons between treatment groups for baseline characteristics were done to ensure comparability between study groups and to identify any possible confounding factors. Categorical outcomes are presented as percentages and were compared between treatment groups with relative risks (95% CI). Continuous outcomes were not distributed normally, so these data are presented as median (IQR) values; treatment groups were compared from the difference in median values, and 95% CIs were derived with a bootstrap procedure. Stratified analyses were done with the Cochran-Mantel-Haenszel statistic. Homogeneity tests (Breslow-Day) were done to assess the association between outcomes and treatment across participating countries. The number needed to harm (95% CI) was calculated for side-effects if a significant difference was recorded. All statistical analyses were done with SAS (version 9.2), and we judged p values of less than 0.05 to be significant.

This study is registered, number ISRCTN34455240.

Role of the funding source

The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the trial data and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 1422 women were enrolled and randomly assigned to receive 600 µg misoprostol sublingually plus standard uterotonics (n=705 participants), or placebo plus standard uterotonics (n=717). Baseline characteristics were similar for participants allocated to each study group (table 1).

Analysis of the primary outcome showed no significant difference in the proportion of women with measured blood loss of 500 mL or more within 60 min after randomisation between the misoprostol and placebo groups (table 2). This result was consistent across the five trial centres (data not shown). Stratified analysis to account for any potential differences between nulliparous and multiparous women did not detect any differences between the treatment groups (data not shown). Stratification by labour induction with and without misoprostol was not done because no participants were induced with misoprostol. Stratified analyses by country did not differ from the previously presented results.

We recorded no significant difference between treatment groups in secondary effectiveness outcomes of: blood loss of 1000 mL or more within 60 min and 90 min after randomisation; blood loss of 500 mL or more within 90 min after randomisation; median blood loss at 60 min; and haemoglobin concentration of less than 80 g/L within 24 h post partum or need for blood transfusion before discharge as requested on the basis of the health provider's clinical judgment (table 2). Additional uterotonics to stop bleeding and avoid the need for blood transfusion after randomisation were given with similar frequency to women allocated to misoprostol and placebo (table 2).

Within 60 min and 90 min after randomisation, shivering was the most common side-effect and was strongly associated with misoprostol (table 3). Furthermore, severe shivering occurred in more women on misoprostol than on placebo. Misoprostol use was also associated with an increased proportion of women who had a temperature of 38°C or higher within 60 min and 90 min after randomisation, a temperature of 40°C or higher within 60 min and 90 min after randomisation, or vomited within 60 min or 90 min after randomisation. Reports of diarrhoea and nausea were infrequent, and differences between the treatment groups were not clinically or statistically significant. Numbers needed to harm suggested that for every three women treated with misoprostol plus standard uterotonics, one additional episode of shivering would be recorded compared with use of standard uterotonics alone. Similarly, for every 35 women treated with misoprostol

	Misoprostol (n=704)*	Placebo (n=717)	Relative risk (95% CI)	Number needed to harm (95% CI)†
Within 60 min after randomisation				
Shivering				
Any	455 (65%)	230 (32%)	2.01 (1.79–2.27)	3.1 (2.7–3.6)
Severe	80 (11%)	7 (1%)	11.64 (5.41–25.03)	9.6 (7.8–12.6)
Temperature				
≥38°C	303 (43%)	107 (15%)	2.88 (2.37–2.50)	3.6 (3.1–4.2)
≥40°C	18 (3%)	3 (<1%)	6.11 (1.81–20.65)	46.7 (29.4–113.6)
Diarrhoea				
Any	2 (<1%)	3 (<1%)	0.68 (0.11–4.05)	..
Severe	0	0	NA	NA
Vomiting				
Any	36 (5%)	16 (2%)	2.30 (1.28–4.09)	34.7 (20.7–107.5)
Severe	2 (<1%)	2 (<1%)	1.02 (0.14–7.21)	..
Nausea				
Any	45 (6%)	35 (5%)	1.31 (0.85–2.01)	..
Severe	2 (<1%)	1 (<1%)	2.04 (0.18–22.41)	..
Within 90 min after randomisation				
Shivering				
Any	514 (73%)	252 (35%)	2.08 (1.86–2.32)	2.6 (2.3–3.0)
Severe	95 (13%)	13 (2%)	7.44 (4.21–13.16)	8.6 (6.9–11.1)
Temperature‡				
≥38°C	406 (58%)	137 (19%)	3.00 (2.55–3.53)	2.6 (2.3–3.0)
≥40°C	48 (7%)	3 (<1%)	16.21 (5.07–51.78)	15.6 (11.6–22.3)
Diarrhoea				
Any	6 (1%)	5 (1%)	1.22 (0.37–3.99)	..
Severe	0	0	NA	NA
Vomiting				
Any	45 (6%)	25 (3%)	1.83 (1.14–2.96)	34.4 (19.6–153.8)
Severe	2 (<1%)	2 (<1%)	1.02 (0.14–7.21)	..
Nausea				
Any	60 (9%)	49 (7%)	1.25 (0.87–1.79)	..
Severe	2 (<1%)	1 (<1%)	2.04 (0.18–22.41)	..

Data are number (%), unless otherwise indicated. ..=data unavailable because of uncertainty between benefit and harm. NA=not applicable. *Blood loss alone was recorded for one patient randomly allocated to misoprostol, and so data are supplied for 704 patients. †Misoprostol plus standard uterotonics versus placebo plus standard uterotonics. ‡Data were recorded for 702 patients receiving misoprostol and 711 patients receiving placebo; outcomes could not be measured in remaining patients.

Table 3: Side-effects

plus standard uterotonics, one additional episode of vomiting would be expected compared with use of standard uterotonics alone (table 3).

18 women had severe maternal morbidity, which was defined as hysterectomy or admission to a maternal intensive care unit (table 2). Two women died, both in the misoprostol group (table 2). One woman was diagnosed with severe post-partum haemorrhage that was unresponsive to treatment, and she died of disseminated intravascular coagulopathy on the day of delivery. The other woman was diagnosed with post-partum haemorrhage that was suspected to be due to uterine atony. She received a blood transfusion and a laparotomy was done under general anaesthesia, at which time a spiral tear of the left lateral wall of the uterus was

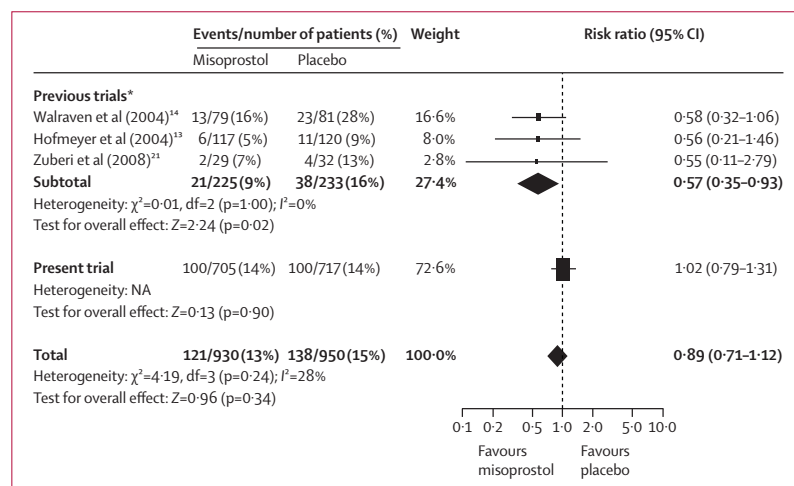


Figure 2: Meta-analysis of blood loss of 500 mL or more within 60 min after randomisation in trials of misoprostol as an adjunct to standard uterotonics for treatment of post-partum haemorrhage
NA=not applicable. *Misoprostol doses were: 400 µg sublingually and 200 µg orally;¹⁴ 400 µg sublingually, 200 µg orally, and 400 µg rectally;¹³ and 600 µg sublingually.²¹

identified and repaired, and the uterine artery was ligated. She was admitted to the intensive care unit for postoperative ventilation, circulatory support, and further blood transfusions, but died the next day from multiorgan failure. The final diagnosis was ruptured uterus and not uterine atony.

Discussion

The results of this large trial show no benefit of misoprostol in addition to standard injectable uterotonics for the treatment of post-partum haemorrhage. Moreover, misoprostol use was associated with shivering, body temperature of 38°C or higher, and vomiting.

Three randomised trials have studied use of misoprostol plus uterotonics versus uterotonics alone for treatment of post-partum haemorrhage: two were published before our study was planned,^{13,14} and one was published while our trial was underway.²¹ Meta-analysis of these three trials found a reduction of 40–50% in blood loss of 500 mL or more in women on misoprostol versus those on placebo (figure 2). The dose and route of administration of misoprostol differed between the three trials, but these differences are unlikely to account for variations in outcome. Variations could possibly be the result of chance since the studies have small sample sizes, and could be compounded by publication bias from other small trials with less optimistic results that have not been published.²² In total, the three trials enrolled 458 women, whereas a major strength of our study is the large sample size (1422 women from five countries) and statistical power. Meta-analysis of the three previous trials and our trial shows a pooled risk ratio of 0.89 for blood loss with misoprostol versus placebo (figure 2). These results underscore the importance of adequately powered large trials since the pooled results of several small trials can

suggest a promising beneficial effect that is not necessarily real.

This trial is limited by several factors. First, post-partum haemorrhage that was suspected to be due to uterine atony was clinically diagnosed and subject to error. Because our trial was pragmatic, misoprostol was given in clinical situations in which it would be used in routine practice had it been shown to be effective. Second, side-effects such as shivering, nausea, vomiting, and diarrhoea were recorded on the basis of women's reports or health-care providers' observations. Last, we were not able to assess the reduction in haemoglobin concentrations after delivery because haemoglobin concentration was not routinely measured before delivery at participating sites. Therefore, the haemoglobin concentration was measured 24 h after delivery only. However, randomisation produced similar study groups for all measured variables, so we do not expect that mean haemoglobin concentrations would have differed between the groups.

Misoprostol is an effective myometrial stimulant post partum, according to findings from physiological studies.^{23,24} It is slightly more effective than oxytocin for induction of labour, but is accompanied by undesirable side-effects, such as uterine hyperstimulation.^{25,26} The absence of effectiveness of misoprostol for treatment of post-partum haemorrhage was an unforeseen result, but is consistent with the unexpected finding that oxytocin is more effective for prevention of post-partum haemorrhage than is misoprostol.⁴ However, the standard uterotonics used in the trial could have caused maximum stimulation of the myometrium such that no further uterotonic effect could be achieved. The trial does not exclude the possibility that misoprostol could be effective in the treatment of post-partum haemorrhage in settings where standard uterotonics are not available. Indeed, findings from two double-blind randomised trials of 40 IU intravenous oxytocin versus 800 µg sublingual misoprostol for primary post-partum haemorrhage have shown that misoprostol is a suitable alternative treatment for post-partum haemorrhage.^{27,28}

The occurrence of two maternal deaths in the misoprostol group is probably a chance finding. As reported in previous trials,^{13,14,21} shivering and pyrexia, both associated with prostaglandin use, were significantly more common in women on misoprostol than in those on placebo. One of the 18 women in the misoprostol group who had temperatures of 40°C or more had delirium. Vomiting also occurred in a significantly higher proportion of women on misoprostol than in those on placebo. In view of the dose-relation of side-effects with misoprostol, future research should use the lowest dose of misoprostol that is judged likely to be effective.

The findings of this trial do not support the use of misoprostol in addition to other conventional uterotonics for the treatment of atonic post-partum haemorrhage. Any further research on misoprostol should focus on the

possible effectiveness of misoprostol in settings where standard uterotonics are not available.

Contributors

MW, JB, GJH, GC, HA-A, PL, NTNN, and BW conceived and designed the study. All authors participated in the trial implementation. DW was responsible for data analysis, and MW, JB, GJH, GC, HA-A, PL, NTNN, DW, and BW interpreted the data. MW, JB, and GJH drafted the report with input and editing from all authors.

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Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

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STUDY PROTOCOL

Open Access

A cluster randomized controlled trial to evaluate the effectiveness of the clinically integrated RHL evidence -based medicine course

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Abstract

Background and objectives: Evidence-based health care requires clinicians to engage with use of evidence in decision-making at the workplace. A learner-centred, problem-based course that integrates e-learning in the clinical setting has been developed for application in obstetrics and gynaecology units. The course content uses the WHO reproductive health library (RHL) as the resource for systematic reviews. This project aims to evaluate a clinically integrated teaching programme for incorporation of evidence provided through the WHO RHL. The hypothesis is that the RHL-EBM (clinically integrated e-learning) course will improve participants' knowledge, skills and attitudes, as well as institutional practice and educational environment, as compared to the use of standard postgraduate educational resources for EBM teaching that are not clinically integrated.

Methods: The study will be a multicentre, cluster randomized controlled trial, carried out in seven countries (Argentina, Brazil, Democratic Republic of Congo, India, Philippines, South Africa, Thailand), involving 50-60 obstetrics and gynaecology teaching units. The trial will be carried out on postgraduate trainees in the first two years of their training. In the intervention group, trainees will receive the RHL-EBM course. The course consists of five modules, each comprising self-directed e-learning components and clinically related activities, assignments and assessments, coordinated between the facilitator and the postgraduate trainee. The course will take about 12 weeks, with assessments taking place pre-course and 4 weeks post-course. In the control group, trainees will receive electronic, self-directed EBM-teaching materials. All data collection will be online.

The primary outcome measures are gain in EBM knowledge, change in attitudes towards EBM and competencies in EBM measured by multiple choice questions (MCQs) and a skills-assessing questionnaire administered electronically. These questions have been developed by using questions from validated questionnaires and adapting them to the current course. Secondary outcome measure will be educational environment towards EBM which will be assessed by a specifically developed questionnaire.

Expected outcomes: The trial will determine whether the RHL EBM (clinically integrated e-learning) course will increase knowledge, skills and attitudes towards EBM and improve the educational environment as compared to standard teaching that is not clinically integrated. If effective, the RHL-EBM course can be implemented in teaching institutions worldwide in both, low-and middle income countries as well as industrialized settings. The results will have a broader impact than just EBM training because if the approach is successful then the same educational strategy can be used to target other priority clinical and methodological areas.

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Background

Research is constantly increasing medical knowledge. For this increased knowledge to be useful in improving the health of populations it should be added to the existing knowledge pool, critically evaluated for validity and implemented by health care professionals. In recent years it is increasingly recognized that improvements in knowledge and skills of health care personnel and improvements in health care outcomes is best accomplished by employing evidence-based medicine (EBM) as part of everyday work. EBM promotes health care decisions based on the current best (valid and relevant) evidence. To achieve this, EBM curricula need to inculcate amongst learners the skills to gain, assess, apply, integrate and communicate new scientific knowledge into clinical decision-making. There is much debate about the effectiveness of various EBM teaching and learning methods and outcomes. Computer-based learning has been shown to be as effective as face-to face, lecture based sessions in improving knowledge [1,2]. There is a lack of consensus, however, as to what methods constitute the best educational practice: a practice that results not only in improvement of basic educational outcomes, such as knowledge and appraisal skills but also in attitudes and behaviour, which, ultimately leads to improved practice [3,4].

Empirical and theoretical evidence suggests that there is a hierarchy of teaching and learning activities in terms of their educational effectiveness: Level 1, interactive and clinically integrated activities; Level 2(a), interactive but classroom based activities; Level 2(b), didactic but clinically integrated activities; and Level 3, didactic, classroom or standalone teaching [3]. Workshop-based teaching, probably one of the most common forms of postgraduate teaching, can at best achieve level 2. Workshops can be interactive but it is the provision of clinically integrated activities that seem to have more sustained effects and have advantages over workshop-based programmes. Such programmes are few and variable in their quality.

A clinically integrated EBM course for teaching postgraduates was developed by the European Union-EBM Unity Project, a consortium of eleven European partners within the framework of Leonardo da Vinci vocational programme of the European Union <http://ebm-unity.pc.unicatt.it/> [5]. This course is learner-centred, problem-based and has integrated e-learning with clinical activities in the workplace. When successfully implemented, the course is designed to provide just-in-time learning through on-the-job-training, with the potential for teaching and learning to directly impact on practice and workplace environment. The course was formally piloted for feasibility in five European countries, in different medical specialties and different languages and tested

in a cluster randomized controlled trial in two countries with promising results [6,7]. However, the generic nature of this course makes application in specific clinical specialties tedious. There is a need to develop specialty-specific courses and to further evaluate this approach rigorously in appropriate settings.

The World Health Organization has published the *WHO Reproductive Health Library* (RHL), an evidence-based specialist library in sexual and reproductive health since 1997. RHL is disseminated extensively in low and middle-income countries to approximately 15,000 users every year. RHL contents are Cochrane systematic reviews in high priority topics mainly in maternal and perinatal health and fertility regulation complemented by commentaries, practical guidance documents and educational videos on techniques to implement effective practices.

In addition, a course on *Evidence-based Decision-making in Reproductive Health* including RHL content has been developed in past years as part of capacity strengthening efforts. This course includes six powerpoint presentations on evidence-based decision-making and a manual with the presentations. Several workshops have been conducted using these materials in the past seven years.

The EU-EBM Unity Project materials were revised to adapt into a sexual and reproductive health context and include RHL as a resource. The revision has made this innovative approach to postgraduate teaching suitable for implementation at obstetrics and gynaecology departments in low and middle-income countries that collaborate with HRP/RHR. As mentioned above, the promising nature of the approach and the relatively weak evidence base to recommend it widely is the principal reason behind the development of this protocol to conduct a RCT to evaluate its effects on various relevant outcomes.

Educational activities within a clinical environment primarily aim to improve the knowledge, attitudes and skills of clinical staff that will lead to improved health care practices and health outcomes of the patients. Given the multitude of educational activities that come in various formats (i.e. didactic, interactive, face-to-face, electronic (1)) it should be an implicit aim of these activities that they result in creating an environment that is more conducive to in-service learning in addition to their more immediate objectives. The context in which these educational activities and learning by staff and students take place is defined as the 'educational environment'. A single educational project may not cause major changes in the educational environment and many other factors related to health system functioning and cultural characteristics may play a role in making the environment more educationally-friendly or not. Nevertheless, measuring the educational environment is important both as an end-point

as well as an explanatory factor for evaluating educational interventions.

Rationale for this trial

Evidence-based reproductive health care requires clinicians to engage with use of evidence in decision-making. To genuinely get involved, healthcare professionals need to effectively incorporate contemporaneous research-based information in the clinical setting. The proposed research project represents part of a continued programme of activities at HRP/RHR aimed at improving the quality of care and capacity-strengthening for evidence-based decision-making in low and middle-income countries. Such research is timely and important because health care workers in many under-resourced settings face difficulties in providing good quality care, keeping their knowledge up-to-date and having the skills to interpret and implement this knowledge. If effective, the clinically integrated e-learning approach can be scaled up without major investment at teaching institutions worldwide. The studies available to date have been exclusively conducted in developed countries. Before engaging in large scale implementation the benefits of this integrated approach should be demonstrated through rigorous research in relevant settings. The hypothesis is that the proposed RHL-EBM integrated e-learning course (experimental group) will improve participants' knowledge, skills and attitude, as well as institutional practice and educational environment, as compared to the use of standard postgraduate educational resources for EBM teaching.

Previous similar studies

We identified a systematic review including 23 studies comparing standalone with clinically integrated teaching in postgraduate teaching in EBM [8]. Most studies reported on knowledge, fewer on skills, (i.e. critical appraisal skills) attitudes and behaviour towards EBM. None of the studies evaluated health outcomes. Results showed that both standalone and clinically integrated courses can improve knowledge. Clinically integrated courses also improved skills, attitudes and behaviour towards EBM. However, the studies included used different teaching methods and assessment tools, and no study compared directly standalone with integrated approach. While the evidence of the review looks promising, more robust evaluation is needed comparing standalone with clinically integrated teaching.

A recent systematic review assessed the effectiveness of EBM teaching on knowledge, skills and attitude/behaviour regarding EBM [9] in postgraduates. The review included 24 studies of different designs, all studies were conducted in developed countries, and most had small sample size and provided little detail about assessment tools and actual intervention. These weaknesses point

towards a need for appropriate sized randomized controlled trials and trans-culturally adapted measurement instruments.

Objectives

The main objective is to evaluate whether the RHL-EBM course is effective in improving knowledge, skills and competencies as compared to passive dissemination of resource materials. A secondary objective is to validate an EBM educational environment tool.

Methods

General

A cluster randomized design is proposed. Such a design is more appropriate for this intervention since the intervention will be implemented at the teaching unit level and the outcome assessments will be measured similarly at the institutional level. In addition, individual randomization can invalidate such an intervention due to contamination [10], whereby control participants have access to and use experimental intervention to enhance their learning if they are working in the same environment.

Participants

Participants are training institutions in obstetrics and gynaecology in the participating countries. Hospitals belonging to the same training institution will form the cluster. Principal investigators from each country will determine the number of potentially eligible training units/clusters in their countries by contacting the head of the specialist training unit and the local authorities (if required). A baseline survey of staffing levels and current postgraduate teaching programmes has been conducted to determine the number of units that can meet eligibility criteria.

Inclusion criteria

Training units that can provide at least four junior residents/registrar (postgraduate trainees) who have not yet been exposed to structured, formal EBM training and who will be available for the duration of the trial will be eligible. Brief descriptive characteristics of each participating junior postgraduate trainee will be collected.

Each institution needs to identify a 'facilitator' who will be able to work with the participants during the trial period. The facilitator will be someone working in the same department with the participants but will be a senior staff member preferably a specialist in obstetrics and gynaecology who is knowledgeable about basic EBM principles.

Recruitment and allocation

The training institutions (clusters) identified by the principal investigators and fulfilling the inclusion criteria will be asked to participate in the trial. The random allocation

Table 1: Intervention 1: WHO RHL EBM clinically integrated e-learning course

Description of the intervention	A course developed in a collaborative project involving 8 international partners. This course is based on the <i>Leonardo da Vinci - Community Vocational Training Action Programme</i> initiated and supported by the European Commission. http://ebm-unity.pc.unicatt.it .
Aim	To familiarise course participants with evidence based medicine (EBM) basics to help incorporate evidence from systematic reviews into practice.
Target participants	Trainee doctors.
Learning objectives	Upon the completion of the course, participants should be competently able to: •generate structured questions arising from clinical problems in practice •search relevant literature, identifying systematic reviews wherever possible •assess the quality (validity) of systematic reviews and primary research included within them •assess the applicability of research findings in clinical practice •identify possible barriers when implementing the output from above activities into clinical practice and apply strategies to overcome them.
Reading/ Learning Resource	A study guide outlining the course and providing learning exercises/assignments and E-learning sessions. 5 modules provide learning materials for undertaking the exercises in the study guide: - Module 1: Asking clinical questions - Module 2: Searching the evidence - Module 3: Critical appraisal of systematic reviews - Module 4: Applicability of the evidence to the patient - Module 5: Implementation of evidence into practice The WHO Reproductive Health Library CD-ROM/ internet version
Learning/ teaching methods	Participant initiated (supported by a facilitator) teaching and learning in a clinical setting Clinical facilitator will guide participants in a clinical setting: •Identifying learning opportunities in a clinical setting •Directing appropriate use of learning resources •Providing feedback on learning exercises/ assignments Participants will pursue independent study using the study guide and e-learning modules directed/ facilitated by the facilitator and will undertake summative assessments.
Student Directed Learning	2 - 3 hours - e-learning.

Table 1: Intervention 1: WHO RHL EBM clinically integrated e-learning course (Continued)

Contact time	20 hours - total including assignments, feedback, and assessments.
Assessments	Feedback on assignments Multiple choice questions to test knowledge Questionnaire to test attitudes OSCE to test competencies Questionnaire on educational environment (EBMEEM).

scheme will be generated at HRP/RHR using computer-generated random numbers. Each cluster will be allocated to either of two groups: RHL-EBM course (intervention 1) or passive dissemination of EBM teaching materials (intervention 2). Due to the nature of the intervention and design it will not be possible to blind the research teams or the participants of their allocated group. However, the participants will only be informed about an educational programme evaluation and will not be told which groups are compared. The individual trainees will receive similar information on a written information sheet.

Interventions

The project aims to evaluate the effects of the experimental intervention (RHL-EBM clinically integrated e-learning course) over passive dissemination of resources that have very similar content and the same learning objectives. It is acknowledged that other EBM teaching activities can also take place independently at the participating institutions. Information on those activities will be recorded systematically. The contents and presentation of both intervention courses were refined and finalized at two meetings of the steering committee that includes experts in research methodology, medical education and obstetrics and gynaecology.

Intervention 1: RHL-EBM Course

The RHL-EBM clinically integrated e-learning course will be the experimental intervention. The course content has been developed following well established guidelines when planning a curriculum [11]. The Course is described in detail in Tables 1 and 2. Briefly, the teaching takes place in the clinical environment and the postgraduate trainee obtains the theoretical knowledge from the interactive e-learning materials, completes assignments and interacts with her/his facilitator throughout the process.

Descriptive information about facilitators' position in the unit, professional qualification and possible EBM teaching activities will be collected. There should be one facilitator per group of 5 to 10 postgraduate trainees. At each training institution one facilitator will be responsi-

Table 2: Details about the activities (intervention)

1. E-learning sessions	The web-based e-learning tools are structured as short <u>sessions</u> (one or more per module) that each can be completed in 15-25 minutes by the participant. These sessions are aimed to give a basic understanding about the concepts involved in each module. Multiple choice questions for self-assessment will be incorporated in the e-sessions.
2. Learning/teaching in a clinical setting	This part is guided by a facilitator during the wardround and includes identification of learning opportunities in a clinical setting. Participants will, by using practical examples, apply the concepts of evidence-based medicine in a real clinical case scenario and be able to discuss with the facilitator and their colleagues.
3. Formative assessment (assignments, OSCE)	The participant needs to complete formative assignments which consist of MCQs, assignments for each module and questionnaires (attitude, educational environment) and OSCEs at the end of the course. After having studied each module, completed assignments need to be sent to the tutor who will provide feedback, which will serve as discussion background between participant and facilitator. The facilitator will decide when the assignment has been completed successfully. OSCEs will need to be completed at the end of the course.
4. Summative assessment	Participants are assessed at the end the course by multiple choice questions (MCQs) which have to be completed pre-course and four weeks after the end of the course. A questionnaire to assess participants' attitudes towards EBM and a questionnaire to assess the educational environment will be taken pre-course (at baseline) and at the end of the course. This will not count towards the participant's overall assessment. Participants will be provided with a password to gain access to the online MCQs. For this, a suitable place at the learner's department or institute providing internet access should be identified. The test has to be taken in presence of the tutor or a person designated by the tutor and the use of additional materials is not allowed. Once the pre-course MCQs have been completed, the participant will have access to the online e-sessions and related materials. Assignments need to be completed for each module before moving on to the next module. Assessment (MCQs for all five modules) will need to be completed at the beginning of the course and at the end.

ble for trial related activities. Facilitators will interact with the participants providing feedback on their assignments, and facilitate discussions during ward rounds/discussions and journal clubs. Facilitators will receive a handbook that will help them to guide the participant.

Intervention 2: Self-directed learning (Passive dissemination of EBM teaching materials)

The RHL-EBM Course will be compared to passively disseminated EBM resources from the WHO RHL workshop-based course that has the same learning objectives. The materials include 6 PowerPoint presentations. The content of the presentations are similar to the content of the RHL-EBM Course. It is detailed described in Table 3. The PowerPoint presentations focus on:

- formulating clinical answerable questions;
- searching effectively for evidence using tools such as the Reproductive Health Library and the Cochrane Library;
- critically appraise clinical evidence for its validity and applicability;
- understanding basic effect measures such as Relative Risk and Numbers Needed to Treat.

The basic differences between experimental (intervention 1) and control (intervention 2) groups are outlined in Table 4.

Outcome measures

The primary outcome measures are:

Gain in EBM knowledge measured by multiple choice questions (MCQs) that have been shown to have face/content validity in relation to course objectives and discrimination capacity in previous studies. Multiple choice questions have been developed by using questions from validated questionnaires and adapting them to the current course [4,12,13].

Change in attitudes towards EBM and competencies in EBM. Attitudes towards EBM will be measured by a validated questionnaire. Previously validated questions to assess attitudes towards EBM will be used [4].

Skills competence in applying EBM principles will be measured by *Objective Structured Clinical Examination* (OSCE). The OSCE is a well established way to assess clinical competency. In this case, EBM-skills related questions following the OSCE structure will be developed for completion electronically.

As a secondary outcome measure, we will assess the educational environment towards EBM by using a questionnaire (EBMEEM). The EBMEEM development is based on previously validated environment measurement tools in different clinical settings [14,15]. The trial will also serve to validate the tool in a larger setting. Trial participants will complete the questionnaire at the beginning and at the end of the course. Only data from the first

Table 3: Intervention 2: Self-directed learning (Passive dissemination of RHL-EBM documents)

Description of the intervention	A course developed by WHO RHR in collaboration with South African Cochrane Centre. This course is implemented either through workshops or simple dissemination of course materials.
Aim	To familiarise course participants with evidence based medicine (EBM) basics to help incorporate evidence from systematic reviews into practice.
Target participants	Trainee doctors.
Learning objectives	Upon the completion of the course, participants should be competently able to: •generate structured questions arising from clinical problems in practice •search relevant literature, identifying systematic reviews wherever possible •assess the quality (validity) of systematic reviews and primary research included within them •assess the applicability of research findings in clinical practice
Reading/Learning Resource	6 Powerpoint presentations WHO Reproductive Health Library CD-ROM/internet version
Learning/teaching methods	Participant initiated learning using electronic resources provided
Student Directed Learning	e-learning (approximately 10 hours learning time)
Contact time	No structured planned contact time. Participants will have access to the online powerpoint presentations for 8 weeks after they have completed the baseline assessment.
Assessments	Multiple choice questions to test knowledge Questionnaire to test attitudes OSCE to test competencies Questionnaire on educational environment (EBMEEM).

completion (baseline) will be used for validation purposes. Data from the second administration at the end of the course will be analysed after determining the items to be included in the validated instrument. Items remaining in the validated instrument will be used to generate baseline scores for the educational environment and to monitor and compare any possible changes at the end of the trial.

Development of the EBMEEM tool

Using the format of previously developed tools the content of the RHL-EBM Course were adapted and included in a draft instrument that yielded 63 Likert-scale items. The items were organized around certain themes namely, learning opportunities; own learning (EBM competence); availability of leaning resources; teachers and teaching (EBM specific); supervision and support; EBM practice (EM atmosphere); and general atmosphere. After several iterations of pilot-testing involving postgraduate trainees in a number of countries and the Steering Committee, the draft instrument to be validated and used in outcome assesment was agreed upon.

Process outcomes such as the experience of the facilitators and the postgraduate trainees will be evaluated through interviews.

Follow-up procedure

The intervention period will be 8-12 weeks. Currently, follow-up beyond the trial period is not planned mainly due to financial constraints. If funds are available a one-year assessment of the EBM educational environment will be considered.

Data management

Data will be collected in the centres using an online data management system developed by the Geneva Foundation for Medical Education and Research (GFMER). Data management will be based at the GFMER, Geneva, Switzerland supervised and monitored by HRP/RHR and Birmingham University.

Data collection will be at baseline (before the intervention), and after completion of the intervention. Data will be recorded by online completion of data forms (MCQs) and questionnaires (attitude, educational environment).

Data entry will be monitored on a day-to-day basis and any problems with logins, missing data and queries will be resolved promptly. The system allows data export to common statistical packages for analysis. It has been agreed that the data files will be exported to an Excel file to be analyzed by the trial statistician in the Statistics and Informatics Services Team at the HRP/RHR.

Analysis plan

Since the random allocation is by teaching units and the inferences will be made at this level, the analysis at the teaching unit will be the unit of analysis.

Table 4: Intervention and control group

	Experimental group	Control group
Before	Introduction and consent MCQs M1-M5 Attitude questionnaire Educational environment measurement tool	Introduction and consent MCQs M1-M5 Attitude questionnaire Educational environment measurement tool
Implement interventions	•RHL EBM course over maximum 8 weeks (5 modules, completion of assignments for each module/week) •Current local teaching	•RHL and workshop-based course materials handed out to each participant •Current local teaching
Assessment	•MCQs: 3-4 weeks after the end of the course •Attitudes: questionnaire 3-4 weeks after the end of the course •Competencies: OSCE 4 weeks after the end of the course •Educational environment: 4 weeks after the end of the course	•MCQs: 12 weeks after baseline assessment •Attitudes: 12 weeks after baseline assessment •Competencies: OSCE 12 weeks after baseline assessment •Educational environment: 12 weeks after baseline assessment

At each participating unit the postgraduate trainees will use the online system to enter their personal data and access the assessment questions (all) and the e-learning modules of the course (either intervention or control materials). The postgraduate trainees will complete the relevant sections at baseline and at the end of the trial period.

Analysis plan for primary outcomes

A score for each individual by dividing the number of points obtained in a test by the maximal number of points that can be obtained will be computed. A summary measure will be obtained for each teaching unit as the mean score for all the individuals taking the test in that unit at baseline (pre-) and post-evaluation phase.

We will compare the knowledge (main outcome) between intervention and control units using analysis of covariance, with pre-test score as a baseline covariate and terms for the stratum and for the group in the model. A 95% confidence interval will be calculated for the difference in knowledge between intervention and control, based on the error term from the analysis of covariance.

We will also compute the change in knowledge as the difference between the post- and the pre-test scores for each individual. A summary measure of the gain in knowledge for each teaching unit will be computed as the mean gain in knowledge. We will compare the gain in knowledge between intervention and control units using analysis of variance, with terms for the stratum and for the group in the model. A 95% confidence interval will be calculated for the difference in gain in knowledge between intervention and control, based on the error term from the analysis of variance.

It is anticipated that in some countries there will be existing formal or informal postgraduate training activities on EBM. These will be reported in the survey of EBM activities that will be conducted before the trial. If data permits a stratified analysis based on the presence or absence of additional basic EBM courses will be conducted. However, it is acknowledged that the study may be underpowered to provide a definitive answer according to the two strata.

Number of subjects and statistical power

There is limited information regarding baseline EBM knowledge and possible knowledge gains and practice changes following implementation of such courses [16]. The evaluation of the pilot course developed within the Leonardo da Vinci pilot project provided some data that were used in the sample size calculation [6,7]. In the pilot evaluation only electronic modules were evaluated as a before and after analysis: For sample size calculations, the standard deviation (SD) for the average gain in knowledge (%) estimated from teaching units/modules means in different countries as SD = 7.9% (likely to be an overestimate) was taken. To allow for random variation of this estimate, a range of SD between 5% and 15% was considered. The power achieved with a total of 60 teaching units to detect a difference in gain of 10% (relative to the maximum score) between two groups in a two-sided test of 5% level, assuming SD = 10%, is 97%. If SD = 12%, the power is 90%. If SD = 14%, the power is 80%. Seven countries: Argentina (4 institutions), Brazil (20), Democratic Republic of Congo (4), India (10), Philippines (10), South Africa (6), Thailand (10) will participate in the trial whose duration is estimated in one year.

Main problems anticipated

Identification of facilitators in the experimental intervention units: The principal investigator will use her/his judgement on the selection of the facilitators and provide training if appropriate. However, the whole philosophy of the Course is for the facilitators to guide the students in the clinical setting and monitor their progress in the process. The facilitators do not need to be EBM experts but rather respected clinicians that could be seen as role models or opinion leaders within their settings.

Internet connectivity

Although all settings will have access to internet for data entry and course content (RHL-EBM) our initial contacts suggest that there may be connectivity problems in some settings like Congo DRC and South Africa. In these settings close monitoring by principal investigators will be required to ensure that emerging problems are solved rapidly.

Existing EBM courses

It is possible that in some of the teaching units there may be other postgraduate teaching activities such as workshops or scientific conferences. It is not possible to control these activities occurring in each setting. The survey conducted before the trial will give information on the scope of the activities likely to exist in each setting. There are two possible protective mechanisms against these activities becoming a threat to the validity of trial results. First, random allocation should ensure that such activities are equally distributed in both groups. Second, stratified analysis based on the presence and absence of existing courses is planned as a secondary analysis.

Expected outcomes of the study

If effective, the RHL-EBM Course will provide an educational intervention that can be scaled up in low and middle-income countries in both teaching and non-teaching institutions. As such it will form a core component to improve quality of care. Discussions with national and international professional organizations to implement the course with formal certification can be performed.

Improvements on knowledge gain, attitudes and skills are important for providing good quality care. Any potential improvement in educational environment will have a major impact on the quality of inservice training not only in resource-poor settings. An original EBM Educational Environment Measurement Tool will be available for all academic or nonacademic settings.

Trial results will be published in a peer-reviewed journal. The results will be disseminated to the participating centres through meetings of the research team with participants at the end of the study. The results will also be

presented and disseminated through the WHO website and the WHO reproductive Health Library (RHL).

Ethics and informed consent

The trial interventions are implemented at the institutional level. Therefore, the primary point at which permission is sought is at the institutional level. Receiving permission from the institution does not constitute a consent on behalf of the participants. It constitutes an administrative agreement between the PI and the institution. A permission sheet will be presented to the person responsible for the institution to be signed. We anticipate that in most cases this person will be the academic head of the obstetrics and gynaecology department.

The facilitators/focal persons and the postgraduate trainees will be informed that one or more educational programme(s) are being evaluated but with no further details. After random allocation each unit will be informed about the activities they should follow including completion of MCQs and other online assessments. We plan to seek consent from individuals within the participating institutions. Individuals will not be identified in the questionnaire. If *intervention 1* is shown to be beneficial in the primary endpoints then it will be provided to all *intervention 2* institutions.

The study protocol was ethically approved by WHO and will also be approved in each participating country.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

RK, KSK and AMG had the original idea for the study and drafted the first version of the research protocol. It was then discussed with all other authors in two meetings in Geneva and the correspondent inputs were added to the protocol. All have read and agreed with the final version of the current study protocol.

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Building capacity for evidence generation, synthesis and implementation to improve the care of mothers and babies in South East Asia: methods and design of the SEA-ORCHID Project using a logical framework approach

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Abstract

Background: Rates of maternal and perinatal mortality remain high in developing countries despite the existence of effective interventions. Efforts to strengthen evidence-based approaches to improve health in these settings are partly hindered by restricted access to the best available evidence, limited training in evidence-based practice and concerns about the relevance of existing evidence. South East Asia - Optimising Reproductive and Child Health in Developing Countries (SEA-ORCHID) was a five-year project that aimed to determine whether a multifaceted intervention designed to strengthen the capacity for research synthesis, evidence-based care and knowledge implementation improved clinical practice and led to better health outcomes for mothers and babies. This paper describes the development and design of the SEA-ORCHID intervention plan using a logical framework approach.

Methods: SEA-ORCHID used a before-and-after design to evaluate the impact of a multifaceted tailored intervention at nine sites across Thailand, Malaysia, Philippines and Indonesia, supported by three centres in Australia. We used a logical framework approach to systematically prepare and summarise the project plan in a clear and logical way. The development and design of the SEA-ORCHID project was based around the three components of a logical framework (problem analysis, project plan and evaluation strategy).

Results: The SEA-ORCHID logical framework defined the project's goal and purpose (*To improve the health of mothers and babies in South East Asia* and *To improve clinical practice in reproductive health in South East Asia*), and outlined a series of project objectives and activities designed to achieve these. The logical framework also established outcome and process measures appropriate to each level of the project plan, and guided project work in each of the participating countries and hospitals.

Conclusions: Development of a logical framework in the SEA-ORCHID project enabled a reasoned, logical approach to the project design that ensured the project activities would achieve the desired outcomes and that the evaluation plan would assess both the process and outcome of the project. The logical framework was also valuable over the course of the project to facilitate communication, assess progress and build a shared understanding of the project activities, purpose and goal.

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Background

Poor health and pregnancy care leads to over half a million maternal deaths and almost eight million perinatal deaths each year. For every woman who dies, about 20 more suffer injuries, infection and disabilities [1]. The burden of death and injury falls disproportionately on low and middle income countries, as is indicated by the lifetime risk of maternal death in South East Asia which is one in 130 compared to one in 7,300 in developed regions [2]. Importantly, much of this burden could be prevented if interventions which have been demonstrated by research to be effective and feasible were implemented at scale [3].

Implementation of the results of research into practice has been identified by the WHO as the most significant challenge to health care [4]. An overview of approaches to bridging the gap between research and practice has highlighted the lack of primary research about what interventions are effective in increasing use of research in health care in low-income settings [5]. In part this reflects the low priority afforded to health services research in these settings [6]. This is a concern given that increasing the generation and use of research in health care are essential steps in improving health systems and achieving better health, particularly in low-income settings [7-9].

Ensuring access to scientifically valid and up-to-date information is a prerequisite to use of research in guiding health care, or 'evidence-based practice'. In spite of the profusion of health information available in print and electronic media (and several international initiatives to promote access), healthcare workers in low-income settings are still disadvantaged when it comes to accessing reliable information on effective care [10,11]. Organisational, financial and technical barriers to accessing research (including lack of computers and internet access, limited scientific literacy, lack of availability of research, inappropriate format of research publications, etc.) and concerns about relevance to local settings are compounded by a lack of skills among practitioners and other stakeholders to appraise and interpret research findings [12].

The South East Asia - Optimising Reproductive and Child Health in Developing Countries (SEA-ORCHID) project aimed to address some of these issues. This five-year project (2004-08) was funded through the International Collaborative Research Grants Scheme, a partnership between the UK-based Wellcome Trust and Australia's National Health and Medical Research Council. The scheme was designed to foster collaborative research between countries in South East Asia and Australia by funding research into major health issues affecting developing countries and developing research capacity.

The objective of SEA-ORCHID was to evaluate whether a intervention designed to strengthen the capacity for research generation, synthesis, and use, improved perinatal practice and led to better health outcomes for mothers and babies.

The SEA-ORCHID study protocol reporting the overall research design and project plan has been published previously [13]. The protocol outlined the core groups targeted by the intervention and key intervention activities. Planning and designing the intervention was undertaken in two stages: development of a project-wide logical framework before the intervention phase; and a site-specific action research-based operationalisation of this framework undertaken during the intervention phase. In this paper, we describe the methods and results of the first stage.

Methods

The SEA-ORCHID project was a pragmatic study that used an uncontrolled before-and-after design to evaluate the impact of a multifaceted tailored educational intervention, implemented within an action research framework (Figure 1). The intervention consisted of a wide range of components and strategies, based on sound educational principles, tailored to meet the needs, priorities and resources of each of the participating hospitals.

The project was approved by the ethics committee relevant to each participating hospital and by the ethics committee of the administering institution in Australia (University of Sydney).

Logical Framework Approach

In complex projects that have broad goals, a logical framework approach can help summarise and describe the multiple strands of the project clearly and systematically, and clarify the core goals, broad objectives, activities and expected outcomes [14]. There are three main components of a logical framework: project rationale (analysis of main problems and their causes); project plan (goal, objectives, activities, outputs) and evaluation and measurement strategy. The logical framework tool helps develop and demonstrate the *logic* of the project in two dimensions. The first, vertical dimension, is whether the activities of the project are likely to achieve the objectives and whether these objectives are likely to achieve the broader goals. The second, horizontal dimension, is whether the evaluation plan will measure the project's progress (process measures) and whether the progress of the project will in turn address the identified problems (outcome measures).

Development of the logical framework

The SEA-ORCHID project coordinator (SM) and one of the Australian-based project staff (CC) managed the

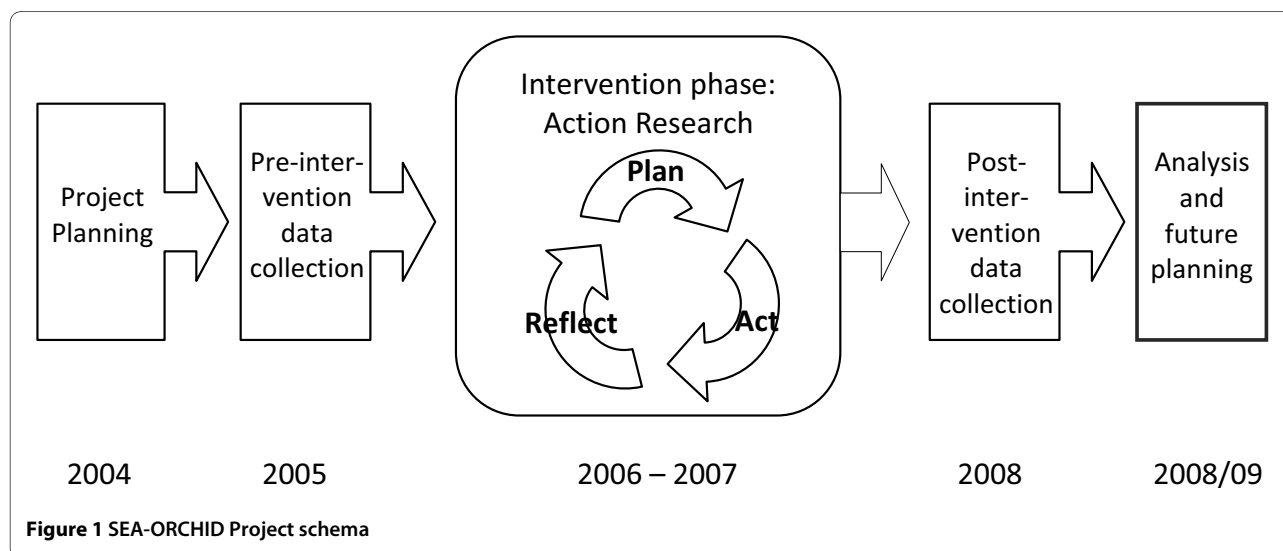


Figure 1 SEA-ORCHID Project schema

development of the logical framework, drawing on information from several sources, along with contributions from members of the SEA-ORCHID team.

Information sources

The information sources used to develop the logical framework included the study protocol [13], a brief survey of perceived current practice, and in-depth discussions at investigator and project meetings (to capture the experiences and perspectives of the local decision-makers). The study protocol set the parameters of the project in terms of its overall aims and design.

At the start of the project planning phase, the SE Asian investigators completed an informal survey of current practice which provided a snap shot of the extent to which care was in line with research (as perceived by the investigators who were senior clinicians working in the participating sites) at different levels within the hospital system in each country (tertiary, regional, provincial and district). The survey also collected data on any complementary research activities that might inform or affect the intervention design, such as participation in the *WHO Reproductive Health Library* cluster randomised trial [15] (Additional file 1: SEA-ORCHID survey).

Discussions at the early investigator meetings were pivotal in articulating the key issues and beginning the process of translating these into objectives linked to activities. At the first full meeting of all the investigators and Australian-based educators in Adelaide in March 2005, several general principles were agreed with respect to intervention planning:

- sustainability and capacity-building should underpin all intervention strategies;
- interdisciplinary teamwork, including both clinical and non-clinical staff, such as librarians and biostatisticians, should be encouraged;

- SEA-ORCHID project baseline data on clinical practices should be used wherever possible to determine local priorities.

During the same meeting, each SE Asian investigator summarised the current situation at the project hospitals in their country in terms of awareness, acceptance and use of research in practice; outlined particular barriers and enablers that could affect the intervention; and suggested activities they considered priorities.

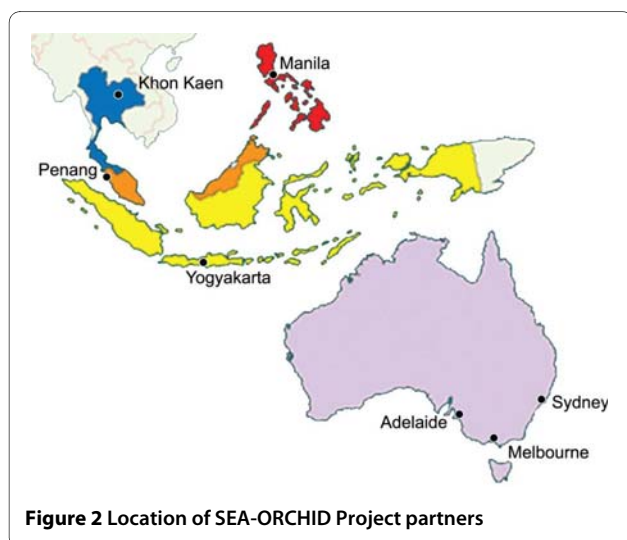
The information from these three sources served as the raw material for the logical framework.

Contributors

The logical framework was developed with input from the seven chief investigators (one from each of the SE Asian countries, and three from Australia), the two project coordinators (from Australia and Thailand) and the Australian project staff.

The SE Asian investigators were senior obstetricians or neonatologists responsible for co-ordinating the project and determining both local and national priorities within the overall framework of the project.

The selection of investigators was determined on the basis of existing partnerships and networks within SE Asia and Australia (Figure 2). Professional links have been fostered over many years through regular meetings of Federation of Asia and Oceania Perinatal Societies and the Perinatal Society of Australia and New Zealand. The participating centres and their respective investigators in Thailand (Khon Kaen University, Khon Kaen), The Philippines (University of the Philippines, Manila) and Indonesia (Gadjah Mada University, Yogyakarta) collaborate on studies initiated by the World Health Organization and are also linked through INCLEN (International Clinical Epidemiology Network) and the Global Network for Perinatal and Reproductive Health. In Thailand, Khon



Kaen University also serves as the co-ordinating base of the Thai Cochrane Network. The participating centre in Malaysia (initially at Ipoh Hospital and then Penang Medical College) is the focal point for initiatives to support and develop Cochrane activity.

The three Australian investigators were from centres that have strong links with The Cochrane Collaboration and international research networks for maternal and perinatal health. The Australian Research Centre for Health of Women and Babies (ARCH) at the University of Adelaide <http://www.health.adelaide.edu.au/og/research/arch.html> comprises several research divisions. The research synthesis division, where the regional co-ordi-

nating unit for the Cochrane Pregnancy and Childbirth Group is based, also includes the ARCTURUS Clinical Trials division and the national coordinating office for the WOMBAT Collaboration <http://www.wombatcollaboration.net> and promotes and supports high quality randomised trials in maternal and perinatal health.

The Centre for Perinatal Health Services Research at the University of Sydney aims to improve the process and outcome of care for mothers and infants in New South Wales, nationally and internationally, through research and education promoting evidence-based practice <http://www.psn.org.au/>. The Centre is also the regional co-ordinating base for the Cochrane Neonatal Group. The third Australian site was at Monash University and houses the Australasian Cochrane Centre <http://www.cochrane.org.au/>, which is responsible for training and supporting review authors and fostering the development of Cochrane activity in Australasia and South East Asia.

The nine study sites (hospitals) were purposively selected to include tertiary referral hospitals (University and regional), provincial hospitals and district hospitals. All were public hospitals and ranged in size from a district hospital in Indonesia with 100 births a month to a tertiary referral hospital in the Philippines with up to 2500 births a month (Table 1). We selected hospitals in which the SEA-ORCHID team members were actively involved in providing clinical services to ensure that the project would be locally owned and that project development, implementation and evaluation would be participatory. The participatory approach to designing the intervention plan did not extend to formal engagement

Table 1: Hospitals in the SEA-ORCHID Project

Country	Hospital site	Type of hospital	Average births per month (in 2005)
Indonesia	Dr Sardjito Hospital, Yogyakarta	Tertiary	100
	Sleman District Hospital, Yogyakarta	District	100
Malaysia	Ipoh Hospital, Ipoh	Tertiary	750
	Kelantan Hospital, Kota Bharu	Tertiary	650
Philippines	Philippine General Hospital, Manila	Tertiary	500
	Jose Fabella Hospital, Manila	Tertiary	2500
Thailand	Srinagarind Hospital, Khon Kaen	Tertiary	200
	Khon Kaen Hospital, Khon Kaen	Regional	300
	Kalasin Hospital, Kalasin	Provincial	350

with local decision-makers or community members who were not actively involved in SEA-ORCHID.

Development process

Development of the logical framework included establishing a project rationale by defining and unpacking the central problem - the problem analysis - and developing a project goal that captured the overarching aim of the project in addressing the central problem.

The project planning component of the process sought to generate a range of possible activities and outputs designed to meet the objectives underpinning the project's overall aim. The third component of the logical framework - evaluation and measurement - outlined the process measures designed to monitor the project's progress and the outcome measures designed to assess whether the project was meeting its goal and purpose.

Refining the logical framework was a four-month, iterative process with drafts circulated among the project teams for feedback and comments. The final version of the logical framework was approved in June 2005.

Results

Project rationale

The starting point for the problem analysis (Figure 3) was the less than optimal reproductive health outcomes in South East Asia, as reflected by high maternal and perinatal mortality. The direct causes of maternal mortality were understood to be unsafe abortions, bleeding, infections, hypertension and obstructed labour; and of perina-

tal mortality were understood to be low birth weight, asphyxia and infection. In response to this, the overarching goal developed for the SEA-ORCHID project was 'To improve the health of mothers and babies in South East Asia'.

Three issues were identified as underlying the central problem of poor reproductive outcomes. These were:

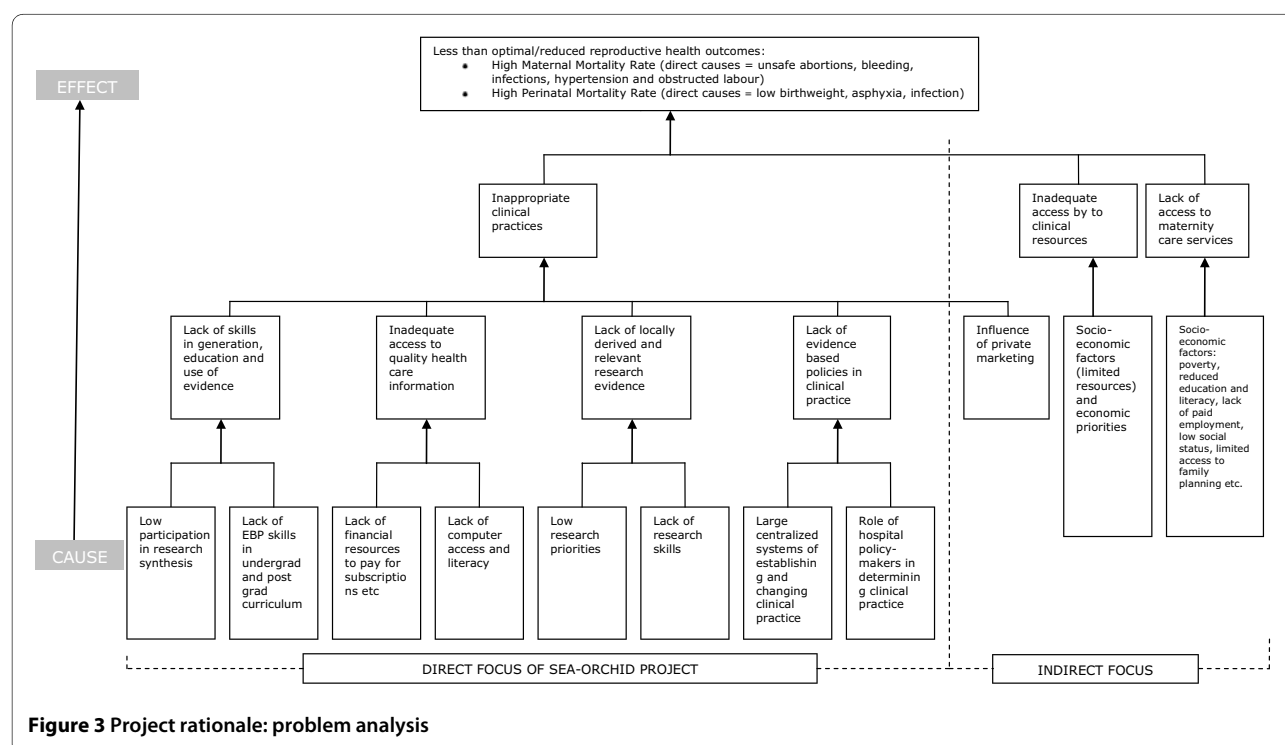
1. Inappropriate clinical practices
2. Inadequate access to clinical resources
3. Lack of access to maternity care services

Since SEA-ORCHID was not a multi-million dollar international aid project, our focus was on the first of these. The purpose of the SEA-ORCHID project was thus defined as 'To improve clinical practice in reproductive health in South East Asia'.

The problem analysis outlined several reasons why clinical practice was not always in line with the results of research. These included a lack of skills in generating and using evidence; inadequate access to reliable healthcare information; lack of locally derived and relevant research evidence; and lack of evidence-based policies and clinical practice guidelines (Figure 3).

These reasons were determined to have several underlying causes:

- low participation in research synthesis
- lack of evidence-based practice training in medical and nursing curricula
- lack of financial resources to pay for subscriptions, etc
- lack of computer access and literacy



- low priority given to research
- lack of research skills
- large centralized systems of establishing and changing clinical practice
- role of hospital policy-makers in determining clinical practice.

Project Planning

In the project planning phase, project objectives were developed to address these underlying causes (Figure 4). The objectives of the SEA-ORCHID project were:

1. to build capacity in research synthesis
2. to increase capacity and skills for evidence-based practice
3. to demonstrate effective implementation strategies for evidence-based practice change
4. to improve access to quality healthcare information
5. to increase locally derived and relevant research activity
6. to increase evidence-based policy making
7. to influence the broader socio-economic and health policy environment.

In relation to the first objective '*To build capacity in research synthesis*', proposed activities included training in systematic reviews and guideline development, developing structures to sustain research synthesis activity in

the longer term, and facilitating recognition of systematic reviews as a valid form of academic research.

Activities linked to the second objective '*To increase capacity and skills for evidence-based practice*' included developing curriculum materials, training educators and users of evidence, and working towards the integration of EBP within existing curricula.

In relation to the third objective '*To demonstrate effective implementation strategies for evidence-based practice change*', activities focused on assessing barriers and educational needs, promulgating adult learning principles, monitoring clinical practice and disseminating findings, and developing collaborative implementation strategies.

The fourth objective '*To improve access to quality healthcare information*' gave rise to activities that included pursuing consortia with medical schools or colleges, promoting access to various professional groups, and developing a longer term strategy to secure national provision to *The Cochrane Library*.

The fifth objective '*To increase locally derived and relevant research activity*' included activities aimed at identifying local research needs and appropriate questions for systematic reviews, facilitating and mentoring those involved in research synthesis, and incorporating research skills into training programs.

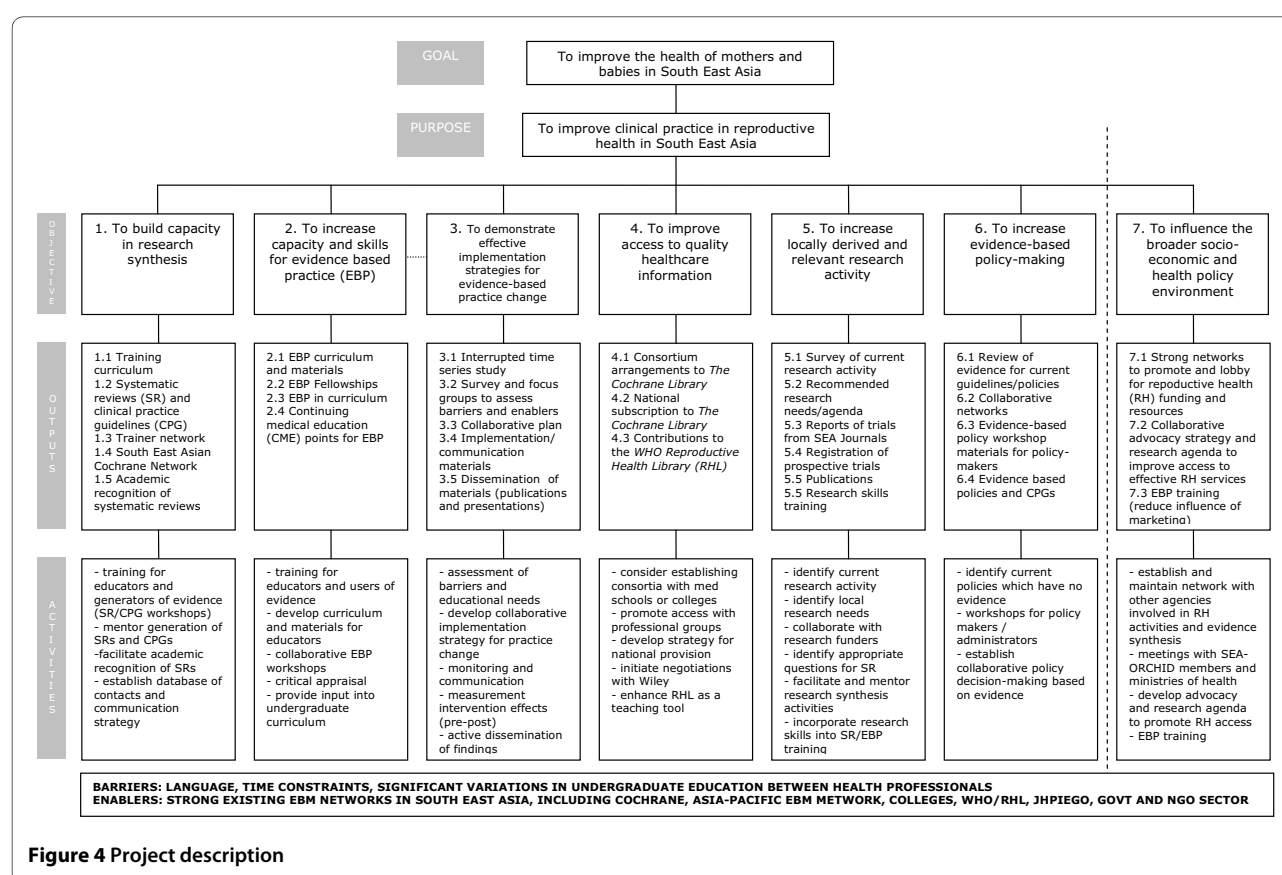


Figure 4 Project description

Activities in relation to objective six *'To increase evidence-based policy making'* included identifying evidence gaps and organising workshops for policy makers.

The final objective *'To influence the broader socio-economic and health policy environment'* was concerned with activities around advocacy and awareness raising, and collaborating with other agencies.

These broad objectives and activity descriptions were used by the project teams in each country and site to develop and implement detailed project plans reflecting local priorities, needs and resources. Descriptions of the specific activities undertaken at each participating hospital are available at <http://www.seaorchid.org>.

Evaluation and measurement

Outcome Measures

To establish whether the project met its goal of improving health for mothers and babies and its purpose of improving perinatal clinical practice, primary outcome measures were designed to evaluate change in maternal and neonatal health outcomes and 15 key evidence-based clinical practices. At each of the participating hospitals we collected data on 1000 births before and after the project intervention to determine changes in health outcomes and practices (Figure 5). Specific outcome measures were also established to evaluate each of the project objectives.

These secondary outcome measures are provided in Table 2.

Process measures

Assessment of the progress of the project was done through face-to-face project meetings, teleconferences and regular reporting. Project meetings involving team members from all SEA-ORCHID sites were held every nine months to provide an opportunity for sharing successes, brainstorming approaches to overcoming barriers, encouraging networking across nodes and refining the planned activities for the next period of the intervention phase. Between project meetings, the Australian educators initiated regular two-monthly teleconferences with each of the project nodes to ensure progress was on track, provide support and resources, and help with any problems or issues that arose. The project investigators also had regular teleconferences. SEA-ORCHID team members reported every two months on the activities undertaken at their hospital by completing activity statements which were then uploaded to the SEA-ORCHID website <http://www.seaorchid.org> to give a cumulative summary of all activities undertaken during the project.

Discussion

There are many different program logic models and frameworks used for planning and evaluating programs.

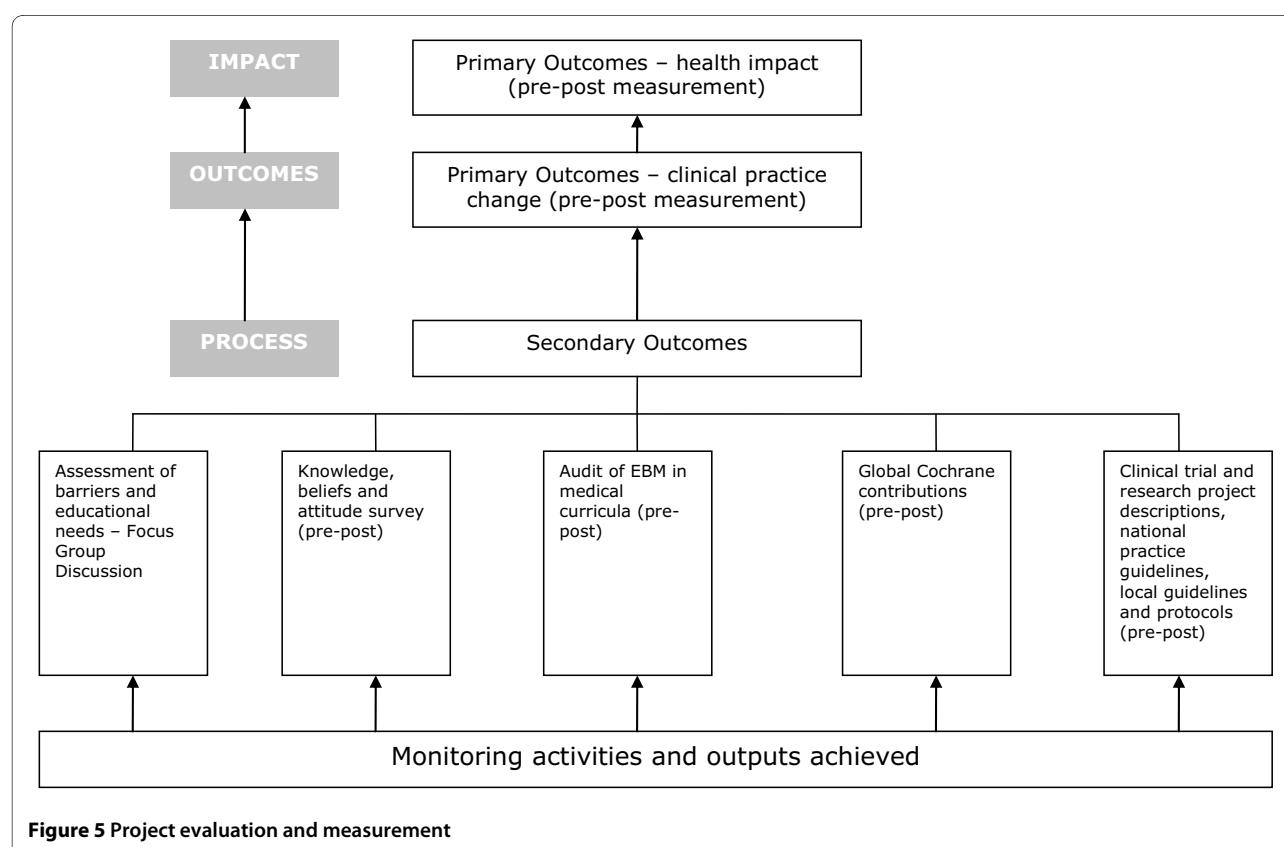


Table 2: Objectives and related outcome measures of the SEA-ORCHID Project

Project Objective	Outcome measures
To build capacity in research synthesis	SR and CPG workshops conducted SRs and CPGs produced SR trainers on database Participants in Cochrane Collaboration Branches of Australasian Cochrane Centre in SE Asia Academic sites recognising SRs in SE Asia
To increase capacity and skills for evidence-based practice	Training materials developed EBP sessions undertaken and number of participants EBP fellowships EBP in curricula pre- and post-intervention Nodes with documented recognition of CME points Persons receiving CME points for EBP training
To demonstrate effective implementation strategies for evidence-based practice change	Pre- and post-intervention measurement of primary and secondary outcomes Qualitative assessment of barriers and enablers to EBP Knowledge, beliefs and attitudes to EBP Program logic framework with input and consensus from all project partners Process evaluation of project implementation Description of collaboration and communication strategies Publication describing current practice
To improve access to quality healthcare information	<i>Cochrane Library</i> usage statistics National subscriptions to <i>Cochrane Library</i> RHL contributions
To increase locally derived and relevant research activity	Research activities Reports of trials identified and submitted to the Cochrane Central Register of Controlled Trials Research trials registered Papers published Training sessions conducted Participants attending training sessions
To increase evidence-based policy making	Description of networking arrangements and communication strategy and members Collaborative activities Workshops conducted Participants attending workshops EB policies and CPGs

Table 2: Objectives and related outcome measures of the SEA-ORCHID Project (Continued)

To influence the broader socio-economic and health policy environment	Documented advocacy strategies
	Advocacy and lobbying networks and activities
	Responses and outcomes to advocacy activities
Systematic Review (SR), Clinical Practice Guidelines (CPG), Evidence-Based Practice (EBP), Continuing Medical Education (CME), WHO Reproductive Health Library (RHL)	

Despite differences in approach, they share a common purpose which is to describe the rationale behind a program and to clarify the relationships between monitoring and evaluation and the project activities. In development projects, logical frameworks are the predominant program logic method used and are particularly important as communication tools in projects that cover diverse countries, cultures and languages [16]. The purpose of using a logical framework in the SEA-ORCHID project was to:

- assess whether the project activities were addressing perceived needs;
- clarify the expected cause-and-effect relationships between the project activities and expected outcomes;
- predict the extent to which the planned outcome measures were likely to evaluate the impact of the project activities; and
- assist project workers to reach a consensus about realistic goals and outcomes of the project.

The logical framework became the core tool that guided the overall intervention strategy and was taken by each site and used as the basis for devising a tailored suite of activities that was implemented within an action research framework during the two-year intervention phase (2006-07). Over the course of the project the logical framework was a powerful tool for facilitating communication within and between sites, and for maintaining a shared understanding of the purpose and progress of a complicated, multilayered intervention.

There are several limitations of the logical framework approach for projects of this nature. Firstly, the linear model does not always do justice to the complex multifaceted influences, dynamic interactions, cultural differences and unforeseen consequences that are part of everyday reality. Therefore they need to be used flexibly and adapted as projects evolve. Secondly, the logical framework only represents the consensus of the individuals involved in developing it. However, they can be used to clarify the assumptions on which project plans are made and allow incoming members of the project to check whether these assumptions are relevant to their local context. Finally, the logical framework approach in

this instance had to be adapted to meet the realities of planning a project intervention within the constraints of a research grant. Under ideal conditions, projects are planned systematically by looking first at the problem, then developing goals and objectives, and finally devising an accompanying evaluation plan [17]. In SEA-ORCHID, the broad issue of building capacity for evidence-based practice and the pre- and post-intervention evaluation strategy was defined first and the specific goals and objectives defined subsequently within the requirements of a research protocol.

Experts in healthcare improvement emphasise the crucial importance of acquiring a good understanding of the problem, the target group, its setting and obstacles to change [5]. Logic models, such as the logical framework, value participatory processes in project planning as a means of achieving this understanding. SEA-ORCHID is an international collaborative project that aims to improve health outcomes for mothers and babies in South East Asia by strengthening capacity for generating, synthesising and implementing evidence. The logical framework approach is an established project design method that is based on a systematic analysis of the problem or situation and an exploration of possible solutions. For SEA-ORCHID, the use of a project-wide logical framework has provided a mechanism for further developing site-specific intervention plans. Overall, this approach is both robust and flexible and appropriate for real-world research into change processes.

Conclusions

The process of developing a logical framework in the SEA-ORCHID project was valuable because it enabled a reasoned, logical approach to the project design that ensured the project activities would achieve the desired outcomes and that the evaluation plan would assess both the process and outcome of the project. The logical framework was also valuable over the course of the project to facilitate communication, provide a reference for assessment of progress and build a shared understanding of the project activities, purpose and goal.

Additional material

Additional file 1 SEA-ORCHID survey.

Abbreviations

EBP: Evidence-based practice; SE Asia: South East Asia; SEA-ORCHID: South East Asia - Optimising Reproductive and Child Health in, Developing Countries; WHO: World Health Organization

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

DH-S, PL, SG and CAC conceived the SEA-ORCHID study. SM and CC devised and refined the logical framework based on contributions from the investigators. SM wrote the initial draft of the manuscript which TT revised. All investigators and Australian educators were involved in developing the design of the project, critically revising the manuscript for intellectual content and have given final approval of the version to be published.

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CLINICAL ARTICLE

Influence of training in the use and generation of evidence on episiotomy practice and perineal trauma

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ABSTRACT

Objective: To examine episiotomy practices before and after a multi-component intervention designed to support the use and generation of research evidence in maternal and neonatal health care. **Methods:** Set in 9 centers across 4 Southeast Asian countries, a retrospective survey was performed for 12 recommended pregnancy/childbirth practices and 13 outcomes of women in each center before and after intervention. Qualitative interviews were conducted to assess staff awareness and experience in evidence-based practice. **Results:** There were significant decreases in the rate of episiotomy, from 64.1% to 60.1% (risk difference [RD] −4.0; 95% confidence interval [CI], −5.8 to −2.2) for all women and from 92.2% to 80.7% (RD −11.5; 95% CI, −13.4 to −9.6) for nulliparous women. Severe trauma decreased from 3.9% to 1.9% (RD −2.0; 95% CI, −2.7 to −1.4) for all women and from 6.7% to 3.0% (RD −3.7; 95% CI, −4.9 to −2.5) for nulliparous women. The frequency of intact perineum increased from 12.4% to 15.6% (RD 3.2; 95% CI, 1.9–4.6) for all women and from 1.7% to 8.0% (RD 6.3; 95% CI, 5.0–7.5) for nulliparous women. **Conclusion:** An intervention based on understanding and using the best available evidence can result in significant improvements in care and health outcomes.

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1. Introduction

Despite being a form of trauma, episiotomy is one of the most common surgical procedures performed on women [1]. High episiotomy rates, some close to 100%, have been reported in North America and Asia [2,3].

Three Cochrane Systematic Reviews provide evidence regarding the practice of episiotomy—comparing restrictive and routine episiotomy [4], suturing techniques [5], and suturing materials [6]. Restrictive episiotomy reduces by approximately 30% severe perineal trauma, need for suturing, and healing complications, without any increase in pain, dyspareunia, or urinary incontinence—despite an almost doubling of the risk of anterior perineal trauma. The benefit of a restrictive practice outweighs the potential harm [4]. If perineal repair is required, a continuous suture results in less pain than does interrupted suturing, although the technique is more difficult [5];

furthermore, the use of synthetic absorbable suture material causes less pain but is more likely to require removal [6].

According to Pakenham-Walsh et al. [7], “providing access to reliable health information for workers in developing countries is potentially the single most cost-effective and achievable strategy for sustainable improvement in health care.” Turning evidence into practice is a complex process; strategies found to be effective include the use of local opinion leaders [8], educational outreach [9], and audit and feedback [10].

The aim of the present study was to examine episiotomy practices used for women undergoing normal vaginal delivery at term in Southeast Asia before and after a multi-component intervention designed to support the use and generation of research evidence in maternal and neonatal health care.

2. Materials and methods

The study was part of the South East Asia Optimising Reproductive and Child Health in Developing Countries (SEA-ORCHID; <http://www.seaorchid.org>) project. The SEA-ORCHID project was designed to

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answer the question “can the health of mothers and babies in Thailand, Indonesia, Philippines, and Malaysia be improved by increasing capacity for the synthesis of research, implementation of effective interventions, and identification of gaps in knowledge needing further research in those countries?”

The present study was undertaken in 9 centers (Khon Kaen University, Khon Kaen Hospital, and Kalasin Hospital in Thailand; Universiti Sains Malaysia and Hospital Raja Permaisuri Bainun Ipoh in Malaysia; Philippines General Hospital and Jose Fabella Hospital in the Philippines; and Dr Sardjito Hospital and Sleman District Hospital in Indonesia) across 4 Southeast Asian countries, with support from 3 Australian Universities (University of Sydney, University of Adelaide, and Monash University). There were 3 main phases to the SEA-ORCHID project, the details and methods for which have been described previously [11]. Briefly, in the first (pre-intervention) phase, primary data were obtained via an audit of 12 areas of recommended practice (including restrictive episiotomy) and 13 health outcomes in pregnancy, childbirth, and neonatal care (including intact perineum). Secondary data were obtained by examining staff knowledge of evidence-based practice, access to evidence, research activity, guideline development, systematic review activity, and undergraduate teaching in evidence-based practice. The second phase comprised an educational intervention, and in the third phase the audit was repeated.

The intervention was tailored to meet the specific needs of each site. It focused on evidence users (clinicians and policy makers), generators (systematic review, guideline development, and improving research infrastructure), and educators (teachers and trainers).

Two or 3 clinical educators from each country, usually mid-career and selected for their ability to act as opinion leaders, underwent a period of training in Australia and then carried out site-specific activities to support building capacity in evidence-based practice tailored to perceived need. Training included interactive evidence-based practice workshops, and some centers used poster displays of evidence, periodic audit, and feedback of rates. All categories of staff were involved. In addition, training was provided on systematic reviewing, guideline development, and input into undergraduate curricula. The academic exchanges consisted of 1–2-month fellowships to the Australian centers for 23 Southeast Asian participants, and teaching tours provided by Australian educators and investigators. The centers did not include specific training on episiotomy, and direct orders to stop or reduce the frequency with which this procedure was performed were not given. Some centers carried out specific training on protecting the perineum without episiotomy, in addition to continuous suturing technique.

The primary audit of 1000 deliveries in each center recorded whether episiotomy was performed, the type of suture material and suture technique used for repair, and the degree of perineal trauma. All women who had a normal vaginal delivery at term were included. Data were extracted from medical records by trained data collectors using a specially designed format, then manually entered into a secure web-based database. Pre-intervention data were collected between April 1 and October 31, 2005, and post-intervention data were obtained between January 1 and June 30, 2008.

Perineal trauma was defined as trauma of the perineum during childbirth that required stitches. Vaginal and perineal tears were classified as follows: first-degree tears involved the vaginal mucosa and connective tissue; second-degree tears included the underlying muscles; third-degree tears involved complete transection of the anal sphincter (confirmed by clinical observation/examination); and fourth-degree tears involved the rectal mucosa. Third- or fourth-degree trauma was classified as severe. Episiotomy was defined as surgical enlargement of the vagina via perineal incision during delivery. The technique of skin closure was classified as either continuous (simple, non-locking, continuous subcuticular sutures) or interrupted (interrupted transcutaneous sutures).

Qualitative data were collected via in-depth interviews conducted during the final 9 months of the intervention (from July 1, 2007, to

February 28, 2008). The interviews were based on a pre-specified protocol and were designed to explore the interviewees' awareness of and experience in undertaking evidence-based practice, carrying out research, and developing guidelines. Two members of the Australian team with experience in qualitative methods and practice change conducted semi-structured face-to-face interviews with maternity and neonatal clinicians at each participating hospital. At each hospital, 2 junior and 2 senior doctors, and 2 junior and 2 senior nurses/midwives were interviewed. In Indonesia and Thailand, interpreters were used during the interviews.

All interviews were audio recorded, transcribed, and anonymized; data were analyzed in emerging themes using NVivo (QSR International, Melbourne, Australia).

Rates were given as percentages, and the difference pre- and post-intervention was described as a risk difference (RD) and a 95% confidence interval (CI) of the RD. This was done for all women and for nulliparous women. Data for each country were pooled and the RD for intact perineum was adjusted for maternal age and parity. $P < 0.05$ was considered to be statistically significant.

The SEA-ORCHID project was approved by the ethics committee at the project administration center, University of Sydney, and at each participating center. Informed written consent was obtained before the interviews were conducted.

3. Results

Data were available for 11 016 women who underwent vaginal delivery at term. The baseline characteristics of women and infants were similar pre- and post-intervention, except for those of nulliparous women in both of the Malaysian centers (Table 1).

Five centers reported a significant decrease in the rate of episiotomy post-intervention, 2 reported no change, and 2 reported a significant increase. The initial rate of episiotomy across all centers was 64.1%, and this decreased to 60.1% post-intervention (RD -4.0 ; 95% CI, -5.8 to -2.2). For nulliparous women, there was a decrease in 6 centers, with the overall rate decreasing from 92.2% to 80.7% (RD -11.5 ; 95% CI, -13.4 to -9.6) (Table 2).

There was a significant increase in the rate of intact perineum in 4 centers, a trend toward significance in 2 centers, and an decrease in 1 centre—resulting in an overall increase from 12.4% to 15.6% (RD 3.2; 95% CI, 1.9–4.6) for all women and from 1.7% to 8.0% (RD 6.3; 95% CI, 5.0–7.5) for nulliparous women. In 1 center, there was a significant decrease in the overall rate of intact perineum, but an increase among nulliparous women (Table 2). When data were pooled for each country, Thailand and the Philippines showed an improvement in the rate of intact perineum; however, the improvement remained significant only for the Philippines after adjustment for parity and maternal age (Table 3).

The pre-intervention rate of severe trauma ranged from 0.0% to 36.9% across the 9 centers. Overall, the rate decreased from 3.9% to 1.9% (RD -2.0 ; 95% CI, -2.7 to -1.4) for all women. This reduction was greatest for nulliparous women: 6.7%–3.0% (RD -3.7 ; -4.9 to -2.5). The rate of severe trauma also decreased for women with and women without episiotomy, with a greater reduction in the latter group (Table 4).

The rate of use of continuous sutures was more than 90% both pre- and post-intervention in 4 centers. Three centers reported a significant decrease in the use of continuous suture, and only 1 experienced a significant increase. The remaining center reported a non-significant increase. Overall, the use of continuous sutures decreased from 71.5% to 63.6% (Table 5).

Chromic catgut was the most common suture material used for perineal repair. Polyglycolic acid was used in 60 (1.2%) of the 5070 pre-intervention births and 429 (9.8%) of the 4358 post-intervention births (Table 5). A change to polyglycolic acid was implemented in 6 centers, 2 of which achieved a significant increase.

Table 1
 Characteristics of women and infants for all full-term normal births in pre- and post-intervention surveys.^{a,b}

	Thailand			Philippines			Malaysia			Indonesia		
	Center 1	Center 2	Center 3	All	Center 1	Center 2	All	Center 1	Center 2	All	Center 1	Center 2
Mother												
Pre-intervention	919 (55.0)	950 (56.4)	956 (55.1)	2825 (55.5)	947 (86.2)	1006 (62.3)	1953 (73.9)	1165 (75.6)	1036 (79.1)	2201 (77.2)	936 (58.7)	1016 (59.1)
Post-intervention	945 (53.3)	970 (49.2)	991 (50.6)	2906 (51.0)	971 (78.6)	944 (52.1)	1915 (65.5)	1103 (61.6)	994 (72.8)	2097 (66.9)	919 (51.8)	984 (54.9)
Maternal age, y												
Pre-intervention	25.6 ± 6.1 (n = 505)	27.5 ± 5.4 (n = 536)	25.5 ± 6.1 (n = 527)	26.2 ± 6.0 (n = 1568)	25.9 ± 6.1 (n = 816)	27.1 ± 6.3 (n = 627)	26.4 ± 6.2 (n = 1443)	28.6 ± 5.8 (n = 881)	30.5 ± 6.3 (n = 819)	29.5 ± 6.1 (n = 1700)	30.1 ± 5.5 (n = 549)	29.5 ± 5.5 (n = 600)
Post-intervention	25.6 ± 6.0 (n = 504)	27.8 ± 5.3 (n = 477)	25.1 ± 5.6 (n = 501)	26.1 ± 5.7 (n = 1482)	27.1 ± 6.6 (n = 760)	27.7 ± 6.3 (n = 476)	27.3 ± 6.5 (n = 1236)	28.6 ± 5.6 (n = 679)	29.9 ± 6.1 (n = 720)	29.3 ± 5.9 (n = 1399)	30.2 ± 5.9 (n = 476)	28.9 ± 5.8 (n = 539)
Gestational age at birth, wk												
Pre-intervention	38.9 ± 1.3 (n = 505)	38.9 ± 1.2 (n = 536)	39.1 ± 1.3 (n = 527)	38.9 ± 1.3 (n = 1568)	38.5 ± 1.0 (n = 816)	38.4 ± 1.0 (n = 627)	38.4 ± 1.0 (n = 1443)	38.9 ± 1.0 (n = 881)	39.0 ± 1.2 (n = 819)	39.0 ± 1.1 (n = 1700)	39.3 ± 1.3 (n = 549)	39.4 ± 1.3 (n = 600)
Post-intervention	38.8 ± 1.2 (n = 504)	38.6 ± 1.0 (n = 477)	38.8 ± 1.2 (n = 501)	38.8 ± 1.2 (n = 1482)	39.1 ± 1.0 (n = 763)	38.5 ± 1.0 (n = 492)	38.8 ± 1.0 (n = 1255)	38.7 ± 1.0 (n = 679)	39.0 ± 1.1 (n = 724)	38.8 ± 1.1 (n = 1403)	39.2 ± 1.2 (n = 476)	38.6 ± 1.0 (n = 540)
Nulliparous												
Pre-intervention	504 (62.9)	536 (49.1)	525 (58.9)	1565 (56.8)	804 (57.7)	626 (46.5)	1430 (52.8)	880 (32.7)	817 (24.0)	1697 (28.5)	549 (40.6)	600 (46.3)
Post-intervention	495 (61.0)	477 (52.0)	500 (57.0)	1472 (56.7)	748 (62.7)	474 (44.5)	1222 (55.6)	678 (27.9)	724 (29.1)	1402 (28.5)	476 (47.1)	540 (50.6)
Total birth												
Pre-intervention	935 (54.5)	961 (55.9)	968 (54.5)	2864 (55.0)	947 (86.2)	1015 (62.2)	1962 (73.8)	1181 (74.9)	1045 (78.9)	2226 (76.8)	945 (58.5)	1031 (58.9)
Post-intervention	957 (52.9)	983 (48.5)	994 (50.4)	2934 (50.6)	975 (78.4)	946 (52.0)	1921 (65.4)	1115 (61.2)	1004 (72.3)	2119 (66.4)	930 (51.2)	994 (54.5)
Birth weight, g												
Pre-intervention	3057 ± 410 (n = 510)	3125 ± 424 (n = 537)	3063 ± 403 (n = 527)	3082 ± 413 (n = 1574)	2894 ± 777 (n = 814)	2919 ± 403 (n = 631)	2905 ± 641 (n = 1445)	3121 ± 422 (n = 885)	3152 ± 465 (n = 824)	3136 ± 443 (n = 1709)	3038 ± 433 (n = 553)	2962 ± 440 (n = 607)
Post-intervention	3104 ± 399 (n = 506)	3133 ± 380 (n = 477)	3070 ± 388 (n = 501)	3102 ± 390 (n = 1484)	2914 ± 433 (n = 764)	2886 ± 402 (n = 492)	2903 ± 421 (n = 1256)	3090 ± 417 (n = 682)	3134 ± 427 (n = 726)	3113 ± 422 (n = 1408)	3035 ± 421 (n = 476)	2956 ± 433 (n = 542)

^a Values given as number (percentage) or mean ± SD.

^b Full-term normal birth was defined as normal vaginal delivery and gestational age more than 37 weeks.

Table 2

Surgical episiotomy rate pre- and post-intervention by center expressed as a percentage of full-term normal births.

Center	Births pre-intervention ^a	Births post-intervention ^a	Episiotomy pre-intervention, %	Episiotomy post-intervention, %	Risk difference (95% confidence interval) ^b	P value ^c
Thailand (all)	1568	1482	91.8	84.1	−7.7(−10.0 to −5.4)	<0.01
Center 1	505	504	95.8	82.9	−12.9(−16.6 to −9.2)	<0.01
Center 2	536	477	92.9	97.3	4.4 (1.8–7.0)	<0.01
Center 3	527	501	86.7	72.9	−14.1(−18.9 to −9.2)	<0.01
Philippines (all)	1274	1237	63.7	62.2	−1.5(−5.3 to 2.3)	0.44
Center 1	777	763	63.6	55.8	−7.8(−12.6 to −2.9)	<0.01
Center 2	497	474	64	72.6	8.6 (2.8–14.4)	<0.01
Malaysia (all)	1700	1403	46	39.3	−6.6(−10.1 to −3.2)	<0.01
Center 1	881	679	60.6	51.1	−9.5(−14.5 to −4.6)	<0.01
Center 2	819	724	30.3	28.3	−2.0(−6.5 to 2.6)	0.40
Indonesia (all)	1146	1016	53.5	51.2	−2.3(−6.5 to 1.9)	0.28
Center 1	546	476	45.2	38.4	−6.8(−12.8 to −0.8)	0.03
Center 2	600	540	61	62.4	1.4(−4.2 to 7.1)	0.63
Total sample	5688	5138	64.1	60.1	−4.0(−5.8 to −2.2)	<0.01

^a Full-term normal birth.^b Figures may not add up owing to rounding.^c Proportion Z test for 2 independent samples.

In total, 75 individual, 25 pair, and 11 group interviews were conducted. Episiotomy was mentioned in 50 interviews, distributed equally across countries. In some hospitals, clinicians reported that practice regarding episiotomy had changed substantially as a result of the project: “Like the episiotomy. I think last time we did routinely do it but, after the introduction of the SEA-ORCHID, now we selectively practice this.”

Several clinicians in other hospitals indicated that they were aware that there was evidence that episiotomy should be undertaken selectively rather than routinely, but that it was still being carried out routinely in their hospitals. One frequently reported reason for routine episiotomy was fear of tearing. Some nurses and junior doctors were concerned about the response of senior doctors if significant tearing occurred when episiotomy was not performed. Episiotomies were preferred to tears because they were easier to repair: “Maybe they are not [relying] on the evidence, because sometimes when we give birth without episiotomy the wound, the vagina, is teared [sic] and it's difficult to repair; that is a bad experience for them.” There was also an increase in difficulties associated with suturing tears following other practice changes such as reducing perineal shaving.

The need for preparation of the perineum (e.g. through perineal massage) was mentioned frequently, and it was suggested by some

clinicians that research into selective episiotomy was applicable to other populations in which women underwent appropriate perineal preparation. The applicability of research into episiotomy in different populations was also questioned for other reasons: “For example, episiotomy because the size of the vagina is different between [local women] and foreigners.”

The need to train junior staff in episiotomy technique was another reported barrier to change in several hospitals: “This hospital is a referral and teaching hospital, so the residents study here...so the episiotomy, they need to do it so [they] know by themselves how to stitch the patients. That's why it is difficult to eradicate episiotomy.”

Several interviewees noted that a lack of time led some clinicians to perform episiotomies unnecessarily: “Sometimes they are impatient. Because you must have patience to wait for patients to deliver normally vaginally, she needs to take time. They want to fasten [sic] the delivery.”

In several hospitals, another barrier to change was the use of outdated protocols still recommending routine episiotomy. Three approaches were suggested as being particularly helpful in terms of changing practice regarding episiotomy. In 2 hospitals at which clinicians believed there had been a successful change in practice, staff had undertaken research projects to investigate the impact of moving from routine to selective episiotomy at the hospital. This was felt to be

Table 3

Rate of intact perineum for full-term normal births for all women and nulliparous women.

Center	Nulliparous				Total sample				
	Pre-intervention, %	Post-intervention, %	RD (95% CI)	P value ^a	Pre-intervention, %	Post-intervention, %	RD (95% CI)	P value (unadjusted) ^a	Adjusted RD (95% CI) ^b
Thailand (all)							2.0 (0.8–3.3)	<0.01	1.3 (−0.8 to 3.3)
Center 1	0.6	2.6	2.0 (0.01–4.0)	<0.05	1.6	4.4	2.8 (0.7–4.9)	<0.01	
Center 2	0.8	0.4	−0.4 (−1.7 to 1.0)	0.60	0.6	0.2	−0.4 (−1.1 to 0.4)	0.38	
Center 3	2.3	2.5	0.2 (−2.3 to 2.6)	0.88	4.2	7.6	3.4 (0.5–6.3)	0.02	
Philippines (all)							12.5 (8.9–16.1)	<0.01	14.8 (2.5–27.1)
Center 1	4.9	30.8	26.0 (21.0–30.9)	<0.01	29.6	38.9	9.4 (4.4–14.3)	<0.01	
Center 2	0.0	9.2	9.2 (5.2–13.3)	<0.01	6.1	23.5	17.3 (12.8–21.8)	<0.01	
Malaysia (all)							−1.1 (−3.8 to 1.6)	0.43	0.5 (−2.8 to 3.8)
Center 1	0.0	1.1	1.1 (−0.4 to 2.5)	0.08	9.3	11.8	2.5 (−0.6 to 5.6)	0.11	
Center 2	1.5	5.7	4.2 (0.6–7.7)	0.03	28.2	22.5	−5.7(−10.0 to −1.4)	0.01	
Indonesia (all)							0.8 (−1.8 to 3.4)	0.54	1.4 (−1.9 to 4.6)
Center 1	1.8	3.6	1.8 (−1.2 to 4.8)	0.25	11.7	13.4	1.7 (−2.4 to 5.8)	0.41	
Center 2	2.2	1.1	−1.1 (−3.2 to 1.0)	0.32	8.1	8.1	0.04 (−3.1 to 3.2)	0.98	
Total	1.7	8.0	6.3 (5.0–7.5)	<0.01	12.4	15.6	3.2 (1.9–4.6)	<0.01	

Abbreviations: CI, confidence interval; RD, risk difference.

^a Proportion Z test for 2 independent samples.^b Adjusted RD for whole-country outcomes only (adjusted for parity and maternal age).

Table 4

Rate of severe trauma pre- and post-intervention for full-term normal births in all women, nulliparous women, and those with and without episiotomy.^a

Item	Pre-intervention	Post-intervention	RD (95% CI)	P value ^b
With and without episiotomy	213 (3.9)	96 (1.9)	−2.0(−2.7 to −1.4)	<0.01
All women	n = 5433	n = 5034		
With and without episiotomy	163 (6.7)	71 (3.0)	−3.7(−4.9 to −2.5)	<0.01
Nulliparous	n = 2418	n = 2337		
Without episiotomy	27 (1.4)	5 (0.2)	−1.1(−1.7 to −0.6)	<0.01
All women	n = 1972	n = 2043		
With episiotomy	186 (5.4)	91 (3.0)	−2.3(−3.3 to −1.4)	<0.01
All women	n = 3461	n = 2991		

^a Values given as number (percentage) unless otherwise indicated.

^b Proportion Z test for 2 independent samples.

important in demonstrating that the results of research conducted elsewhere also applied locally.

Changes in financial incentive were also noted as being effective at modifying episiotomy practice: “[Before] if you put...‘vaginal delivery’, that may not be compensated. But, if you put maybe ‘episiotomy and repair,’ it will be compensated. So now they don’t compensate [episiotomy] anymore...you can only provide normal delivery and you will be compensated.”

Finally, several clinicians mentioned the value of visits to other hospitals, undertaken by themselves or colleagues, to witness firsthand that selective episiotomy was safe.

4. Discussion

In the present study, a multi-component intervention centered around understanding and using the best available evidence resulted in significant improvements in restrictive episiotomy practice and an increase in the rate of intact perineum in both parous and nulliparous women undergoing vaginal delivery at term.

Before the intervention, episiotomy rates were high in 8 of the 9 centers, and across all centers almost all nulliparous women underwent episiotomy. Following the intervention, although significant reductions were achieved, rates were still high. In a survey of Canadian hospitals practicing restricted episiotomy, the median rates reported were 62% for nulliparous and 40% for multiparous women [12]. In 1989, 39% of women undergoing vaginal delivery in the USA underwent episiotomy [1], compared with 28%–83% in the present study. It was gratifying that all centers reporting a decrease in the rate of episiotomy experienced an increase in the rate of intact perineum, which was associated with an overall reduction in the rate of severe trauma among both the women who underwent episiotomy and those who did not. Although the 2.9% increase in the rate of intact perineum (9.2% for nulliparous women) corresponded to thousands of women in Southeast Asia experiencing childbirth without the pain and complications of episiotomy, there are still many more women who could benefit from this intervention. Similarly, although this improve-

ment translated into less use of resources and health practitioner's time, further reductions are possible.

The fact that each center designed and implemented their intervention could explain the wide variation in RD pre- and post-intervention. The intervention focused on the skills needed to understand and implement evidence, resulting in a varied emphasis on specific practices depending on perceived needs. This could also be the reason why some centers reported no decrease or even an increase in episiotomy rate. In addition, it might explain why the overall decrease in episiotomy rate (from 64.1% to 60.1%) was modest. However, the advantage of this approach is that centers now have the skills to identify and implement new evidence. An unexpected benefit was that episiotomy rate was included as a national indicator in the Quality Improvement Programme of Malaysia. Thus, Malaysia could expect a decrease in episiotomy rate nationwide.

The intervention period was 2.5 years, and some changes may take longer to implement: for example, changes to midwifery and undergraduate medical curricula/subsequent graduation of students taught the new curricula. Furthermore, teachers of restrictive episiotomy practice also require initial training on conducting a normal birth without perineal trauma. This was evidenced by the fact that data collection at 1 of the centers at which there was an increase in episiotomy rate coincided with the entry of new residents trained in routine episiotomy. In addition to differences in intervention, differences in the enthusiasm of key staff could contribute to the wide variation seen between centers.

Several centers attempted to change from catgut to synthetic suture material, but the associated cost prohibited implementation in most centers. In 1 country, it was discussed at national level and a decision was made that it was too expensive to implement. In 2 countries, patients had to pay for the suture material themselves; despite this, 2 centers reported a significant change (data not shown).

The interviews identified a range of barriers to restrictive episiotomy practice. These included fear of tearing, difficulty in repairing tears compared with cuts, lack of perineal preparation, applicability of research carried out in a different population, lack of time, and need to train junior staff. Fear of tearing and difficulty associated with repair were reasons for episiotomy originally being introduced. The applicability of evidence between different populations is a valid concern, and it is reasonable to query whether there could be anatomic differences in perineal structure among Southeast Asian women that might affect applicability. Higher rates of episiotomy and perineal trauma have been reported for Asian women than for non-Asian women [13–16]. One center had successfully implemented restricted episiotomy practice pre-intervention. During the study, most centers were able to implement a restrictive practice without an increase in severe trauma and, in fact, many experienced a decrease. The results show that evidence for restricted episiotomy can be applied beneficially to Southeast Asian populations.

In conclusion, an intervention to increase the use and generation of evidence can result in significant improvements in episiotomy practice and a reduction in the rate of perineal trauma among women. The model could be adapted to improve the uptake of evidence-based practice in other centers and in other disciplines.

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Table 5

Suture material and technique used for skin closure at all centers for full-term normal births.^a

Item	Pre-intervention (n = 5070)	Post-intervention (n = 4358)
Polyglycolic acid	60 (1.2)	429 (9.8)
Continuous suture	3624 (72)	2775 (64.0)
Continuous suture using polyglycolic acid	57 (1.1)	208 (4.8)

^a Values given as number (percentage) unless otherwise indicated.

Ussahgij; Bussarin Khianman; Bunpode Suwannachai; Thitiporn Siriwachirachai; Ussanee Swadpanich; Resti Bautista; Geraldine Castillo-Torralba; Valerie Guinto; Cristina Crisologo; Maria L. Andal; Cynthia Anzures; Gina Canceran; Alvin Chang; Chun Wearn Koh; Japaraj Peter; Zabidah Mat Sidi; Sivasangari Subramaniam; Che Anuar; Tan B. Geok; Noraida Hassan; Hans Van Rostenberghe; Diah R. Hadiati; Tunjung Wibowo; Setya Wandita; Fauziah Basuki; and Nawang Purwanti.

Conflict of interest

The authors have no conflicts of interest.

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Air vs Perfluoropropane Gas in Pneumatic Retinopexy

A Randomized Noninferiority Trial

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Objective: To evaluate whether air is as effective as perfluoropropane gas in treating rhegmatogenous retinal detachment by pneumatic retinopexy.

Methods: In a double-blind, randomized, clinically controlled noninferiority trial, eligible patients were randomized into 2 treatment groups by using block randomization and treated by pneumatic retinopexy using filtered air or perfluoropropane gas.

Main Outcome Measures: Retinal reattachment rate and final visual recovery.

Results: One hundred twenty-six patients were recruited. Half (63 patients) were assigned to receive filtered air during pneumatic retinopexy and half received perfluoropropane gas. The single-procedure reattachment rate was higher for the perfluoropropane gas group (73.0% [46 patients]) than for the air group (60.3% [38]), but the difference was not statistically significant (risk difference, -12.7%; 95% confidence interval, -29.0% to 3.6%). The final reattachment rate after additional pneu-

matic retinopexy and/or surgical procedures was 92.1% (58) in the air group and 96.8% (61) in the perfluoropropane gas group. This result showed an equivalent effect on the final reattachment rate (risk difference, -4.7%; 95% confidence interval, -12.7% to 3.2%). Final visual acuity did not differ significantly between groups.

Conclusion: Pneumatic retinopexy using filtered air is associated with a nonsignificantly lower initial reattachment rate than using perfluoropropane gas but results in an equivalent final reattachment rate and final visual recovery.

Application to Clinical Practice: Air is an acceptable alternative to perfluoropropane gas when treating rhegmatogenous retinal detachment by pneumatic retinopexy.

Trial Registration: clinicaltrials.gov Identifier: NCT00120445

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PNEUMATIC RETINOPEXY IS A commonly used technique to repair rhegmatogenous retinal detachment (RRD). In this procedure, a gas bubble is injected into the vitreous cavity and placed over the retinal break by manipulating the patient's head position. The break is closed, and retinopexy seals the break.^{1,2} Subretinal fluid is then reabsorbed by the retinal pigment epithelium. This technique has several potential advantages in the management of uncomplicated RRD. It has been shown that pneumatic retinopexy involves less tissue manipulation, has less morbidity, and has better functional visual results compared with scleral buckling and vitrectomy.³⁻¹¹ Some researchers used air instead of expansile gas in an attempt to minimize vitreous disturbance and reported satisfactory results. Carim¹² demonstrated

that using air in pneumatic retinopexy was successful in selected cases. Yospaiboon and Sajjapong¹³ also reported satisfactory results using filtered air in this procedure, particularly in patients with phakic eyes. The reattachment rate and visual recovery were comparable to those when using expansile gas.

To the best of our knowledge, no clinical trial has compared air and expansile gas in pneumatic retinopexy. We hypothesized that both air and expansile gas are similarly effective as agents in pneumatic retinopexy. Perfluoropropane (C₃F₈) gas is expensive, and, in settings where C₃F₈ gas is not available or affordable, such as developing countries or remote areas, air would be a reasonable alternative. Therefore, we conducted a double-blind, randomized, controlled study to evaluate whether air is as effective as C₃F₈ gas in treating RRD by pneumatic retinopexy. We

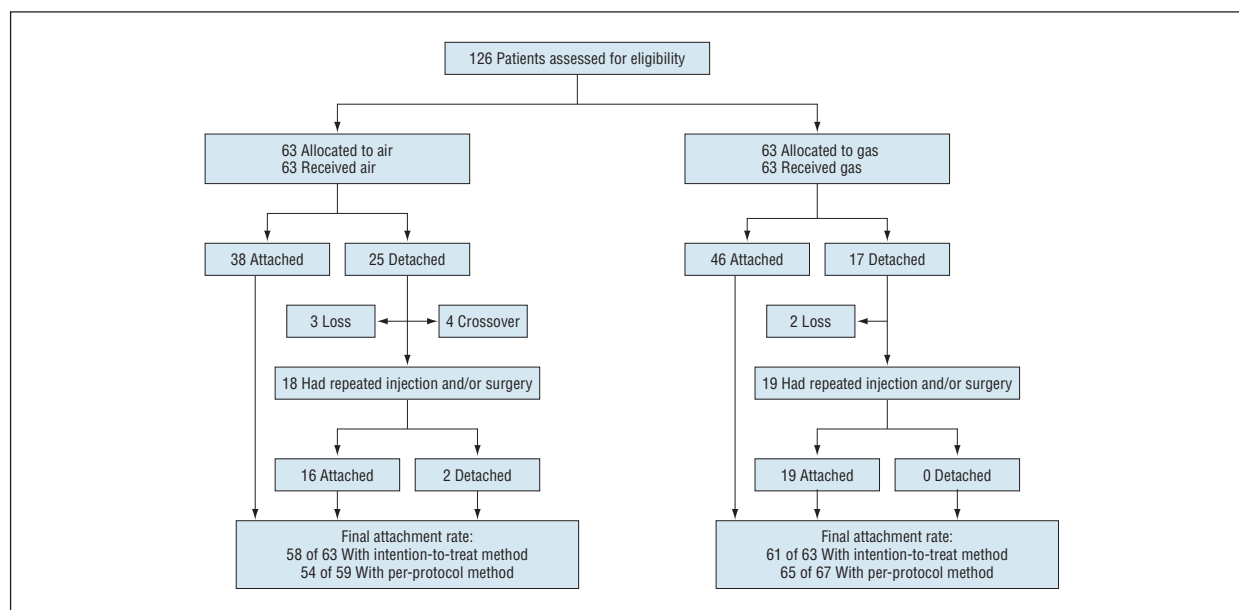


Figure 1. Study flowchart.

selected C_3F_8 gas because it was commonly used for pneumatic retinopexy at our hospital.

METHODS

A hospital-based, double-blind, randomized, clinically controlled noninferiority trial was conducted in a vitreoretinal center at Srinagarind Hospital, Khon Kaen University, in Thailand. This trial followed the tenets of the Declaration of Helsinki and was approved by the Khon Kaen University Ethics Committee for Human Research. All patients with RRD who visited the center between April 1, 2004, and October 31, 2008, were recruited. The eligibility criteria were having a superior retinal break between the 8-o'clock and 4-o'clock positions, having a single retinal break not larger than 2.5 clock hours, having multiple breaks not more than 3 clock hours away, having no or minimal proliferative vitreoretinopathy (PVR), being able to physically and mentally cooperate in postoperative head positioning, having at least 12 weeks of follow-up, and being capable of giving informed consent. Patients were excluded if they had only 1 eye or had ocular media opacities, advanced glaucoma, aphakia, pseudophakia, or a history of previous ocular surgical procedures. Recruited patients were allocated into 2 groups by block randomization with varying block size. Patients were treated by pneumatic retinopexy using filtered air or C_3F_8 gas (**Figure 1**).

One surgical nurse (S.P.) prepared air and C_3F_8 gas for intravitreal injection. An insulin syringe was connected to a filter (Millipore; Bausch & Lomb Inc, Rochester, New York) that had the capacity to filter bacteria at a level of $0.22\ \mu m$,¹⁴ and 0.3 mL of filtered air or C_3F_8 gas was drawn into the syringe. Syringes were then coded A or B for use in the treatment of patients in the air or C_3F_8 gas group, respectively. The allocation sequence was generated using computer-generated random numbers with randomly varying block size (SAS statistical software; SAS Institute Inc, Cary, North Carolina). The random allocation sequence was concealed in a sealed opaque envelope, numbered sequentially, and kept by the surgical nurse, who was the only one who knew which code was for air or C_3F_8 gas. The researchers and patients did not know the code, and unblinding was done at the end of the study.

The primary outcomes for both groups were the retinal reattachment rate and the final visual recovery. The retinal reattachment rate was calculated from the number of patients who had an attached retina after surgery divided by the total number of patients treated. The final visual recovery was the difference between the preoperative and postoperative best-corrected visual acuity that improved by 1 or more lines on a Snellen acuity chart was classified as "improved"; postoperative best-corrected visual acuity that decreased by 1 or more lines was classified as "worse."

We considered this an equivalence trial; thus, a formula by Jones et al¹⁵ was used for sample size calculation. We estimated that both groups would have a 90% final reattachment rate. At a 95% confidence level and a power of 80%, an acceptable margin of noninferiority in effectiveness of treatment was 15% for a 1-tailed test. The required number of patients per treatment group was calculated to be 63. For a 1-tailed test, equivalence is declared if the lower 1-sided confidence limit exceeds the defined level. We chose to use the 1-sided test in this study because we wanted to confirm that pneumatic retinopexy using air is not inferior to the procedure using C_3F_8 gas. Equivalence and superiority were both regarded as positive outcomes.

Descriptive statistics were used for the patients' demographic characteristics and clinical findings. Intention-to-treat and per-protocol methods were used to analyze the results and the comparisons between air and C_3F_8 gas. The reattachment rate, final visual recovery, and risk difference with 95% confidence intervals (CIs) were used to compare the differences for categorical outcomes.

RESULTS

A total of 126 patients with RRD were recruited into the trial. We allocated 63 patients to the air group and another 63 patients to the C_3F_8 gas group (**Figure 1**). The demographic characteristics of the patients in each group, including age and sex, and the associated conditions, such as myopia and history of trauma, were similar at study entry. The clinical findings in each group, including the duration of symptoms, type and number of retinal breaks,

Table 1. Demographic Characteristics and Clinical Findings

Characteristic	No. (%) of Patients	
	Air Group (n=63)	C ₃ F ₈ Gas Group (n=63)
Age, mean (SD) [range], y	54.1 (11.3) [28-76]	52.6 (13.5) [16-72]
Sex		
Female	21 (33.3)	20 (31.8)
Male	42 (66.7)	43 (68.2)
Associated conditions		
Myopia	6 (9.5)	5 (7.9)
Trauma	5 (7.9)	3 (4.8)
Duration of symptoms, mean (SD), wk	3.8 (4.0)	4.2 (5.8)
No. of retinal breaks, mean (SD)	1.4 (0.7)	1.4 (1.0)
Extent of detachment, No. of quadrants		
1	7 (11.1)	7 (11.1)
2	22 (34.9)	34 (54.0)
3	24 (38.1)	15 (23.8)
Total detachment, PVR grade ^a	10 (15.9)	7 (11.1)
A	41 (65.1)	41 (65.1)
B	21 (33.3)	21 (33.3)
C1	1 (1.6)	1 (1.6)

Abbreviations: C₃F₈, perfluoropropane; PVR, proliferative vitreoretinopathy.^aGrading of PVR is explained in Tornambe et al.¹⁶**Table 2. Pneumatic Retinopexy and Surgical Procedures**

	No. (%) of Patients	
	Air Group (n=63)	C ₃ F ₈ Gas Group (n=63)
Pneumatic retinopexy, No. of injections ^a		
Single	38 (60.3)	46 (73.0)
Multiple	25 (39.7)	17 (27.0)
Complications	12 (19.1)	13 (20.6)
New or missed break	3 (4.8)	8 (12.7)
Subretinal gas	4 (6.3)	1 (1.6)
Glaucoma	0	2 (3.2)
Epithelial defect	2 (3.2)	0
Other	3 (4.8)	2 (3.2)
Surgical procedures	24 (38.1)	20 (31.8)
Pars plana vitrectomy	19 (30.2)	12 (19.1)
Scleral buckling	1 (1.6)	6 (9.5)
Combined procedure	4 (6.3)	2 (3.2)
Follow-up, range, wk	6-228	6-190

Abbreviation: C₃F₈, perfluoropropane.^a*P* < .001.

extent of the detached retina, and grading of PVR, were also similar (**Table 1**). The interventions, including pneumatic retinopexy and other surgical procedures, are given in **Table 2**. Patients in the air group needed statistically significantly more injections (*P* < .001) than did those in the C₃F₈ gas group.

In this study, the initial reattachment rate for the air group was 71.4% (5 of 7 patients) for those with a retinal detachment extending 1 quadrant, 63.6% (14 of 22) for those with a retinal detachment extending 2 quadrants, 66.7% (16 of 24) for those with a retinal detachment extending 3 quadrants, and 30.0% (3 of 10) for those

Table 3. Reattachment Rate and Final Visual Recovery

	No. (%) of Patients		Risk Difference (95% CI)
	Air Group (n=63)	C ₃ F ₈ Gas Group (n=63)	
Reattachment rate			
Initial	38 (60.3)	46 (73.0)	-12.7 (-29.0 to 3.6)
Final	58 (92.1)	61 (96.8)	-4.7 (-12.7 to 3.2)
Final visual recovery			
Improved	33 (52.4)	36 (57.1)	-4.8 (-2.2 to 12.6)
Stable	23 (36.5)	18 (28.6)	7.9 (-8.4 to 24.2)
Worse	7 (11.1)	9 (14.3)	-3.2 (-14.8 to 8.4)

Abbreviations: C₃F₈, perfluoropropane; CI, confidence interval.

with total detachment. The initial reattachment rate for the C₃F₈ gas group was 85.7% (6 of 7 patients) for those with a retinal detachment extending 1 quadrant, 67.6% (23 of 34) for those with a retinal detachment extending 2 quadrants, 66.7% (10 of 15) for those with a retinal detachment extending 3 quadrants, and 100% (7 of 7) for those with total detachment.

The incidence rate of complications was 19.0% (12 of 63 patients) in the air group and 20.6% (13 of 63) in the C₃F₈ gas group (**Table 2**). There was no statistically significant difference in the number of complications from pneumatic retinopexy between the groups. Of interest, the incidence of new or missed breaks was 4.8% (3 patients) in the air group and 12.7% (8 patients) in the C₃F₈ gas group.

After the initial procedure, 4 patients in the air group in whom the reattachment failed were treated with C₃F₈ gas. Following the intention-to-treat principle, we did not exclude these 4 patients who crossed over from the analysis. Three patients in the air group and 2 in the C₃F₈ gas group were lost to follow-up. We assumed that they left the study because of an unsatisfactory result, and we included these patients in the group with detached retinas during analysis. Retinal reattachment rates evaluated after a single procedure were 38 of 63 patients (60.3%) in the air group and 46 of 63 (73.0%) in the C₃F₈ gas group (**Table 3**). The difference in initial reattachment rates was -12.7% (95% CI, -29.0% to 3.6%), which was not statistically significant (**Figure 2**). The final reattachment rates after repeated pneumatic retinopexy and/or additional surgical procedures were 92.1% (58 of 63 patients) in the air group and 96.8% (61 of 63) in C₃F₈ gas group. The difference in final reattachment rates was -4.7% (95% CI, -12.7% to 3.2%), indicating an equivalent effect of air and C₃F₈ gas on the final reattachment rate.

Although the intention-to-treat method can preserve the value of the randomization, substantial discontinuation or crossover between treatments will cause it to underestimate the magnitude of the treatment effect. Therefore, using intention-to-treat analysis might make the groups more similar and increase the likelihood that the treatments will be equivalent. We also used the per-protocol method to analyze our data. The final reattachment rates after repeated pneumatic retinopexy and/or surgical procedures were 91.5% (54 of 59 patients) in the air group and 97.0% (65 of 67) in the C₃F₈ gas group.

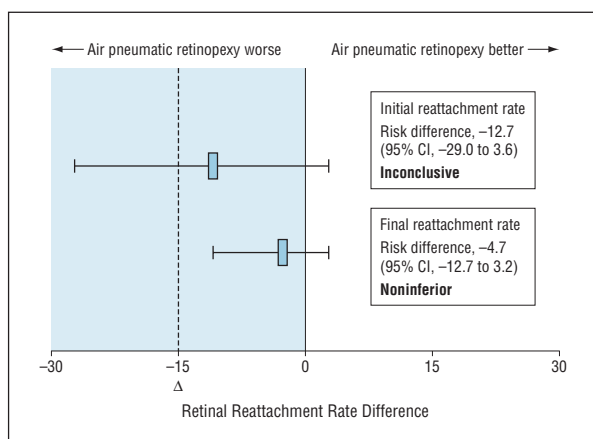


Figure 2. Retinal reattachment rate difference, determined by subtracting the perfluoropropane treatment reattachment rate from the air treatment reattachment rate. The vertical dotted line represents the margin of clinical equivalence; the vertical solid line, the null effect; and the error bars, 2-sided 95% confidence intervals (CIs). The shaded area indicates the zone of inferiority. For the initial reattachment rate difference (upper bar), the 95% CI includes Δ (which indicates the acceptable margin of noninferiority in effectiveness of treatment) and zero, and the difference is nonsignificant but the result regarding noninferiority is inconclusive. For the final reattachment rate difference (lower bar), the 95% CI extends to the right of Δ and includes zero, and the air treatment is noninferior but not shown to be superior.

The difference in final reattachment rates was -5.5% , which was similar to the result from the intention-to-treat analysis. This similarity indicates that pneumatic retinopexy using air is noninferior but not superior to retinopexy using C_3F_8 gas. In other words, there was an equivalent effect on the final reattachment rate. Final visual acuity results were slightly better in the C_3F_8 group compared with the air group, but the difference was not statistically significant ($P = .61$) (Table 3).

COMMENT

The results of this study demonstrate that final visual acuity and reattachment rates after pneumatic retinopexy for RRD were similar when using filtered air or C_3F_8 gas. This finding agrees well with previous studies.^{3,16,17} In a collaborative study of 100 cases, Hilton and coworkers³ demonstrated a reattachment rate of 78% after a single pneumatic retinopexy using C_3F_8 gas, with subsequent procedures resulting in a final reattachment rate of 98%.

Partial vitreal gas filling induces both biochemical and structural alterations and might predispose the eye to PVR, epimacular membrane, and new or missed break formation. From the previous reports, PVR was 5.2%, epimacular membrane was 2% to 4%, and new or missed retinal break formation was 11.7%.¹⁸ Therefore, some researchers used air in an attempt to minimize vitreous disturbance and reported satisfactory results. In 1990, the idea of using nonexpanding gas of short duration in pneumatic retinopexy was first introduced by Carim.¹² He used variable amounts of air (up to 1.0 mL) and had a reattachment rate of 75%. Three years later, Sebag and Tang¹⁹ performed pneumatic retinopexy using 0.8 mL of filtered air, with a reattachment rate of 87% (39 of 45 patients) after a single intravitreal injection. In that case series, paracentesis of the anterior chamber was performed

in all patients. Yospaiboon and Sajjapong¹³ also demonstrated a reattachment rate of 75% following a single injection of 0.3 mL of air for pneumatic retinopexy, with a final reattachment rate of 90% after subsequent procedures. The reattachment rate in phakic eyes was 88% following a single air injection and 94% after subsequent procedures. They concluded that pneumatic retinopexy with air can be performed in selected cases of phakic retinal detachment with a success rate that is comparable to that of the procedure using expansile gases.

Two gas properties, surface tension and buoyancy, play roles in the mechanism of pneumatic retinopexy. A gas bubble occludes the retinal break, permitting the retinal pigment epithelium to remove subretinal fluid, and then presses the retina against the retinal pigment epithelium, sheltering the edge of the break from eddy currents until a chorioretinal scar is formed, sealing the break. Generally, mild chorioretinal adhesion after laser photocoagulation occurs within 24 hours, moderate adhesion in 5 to 7 days, and strong adhesion in 10 to 14 days. Because moderate chorioretinal adhesion was noted 5 to 7 days after retinopexy, the air bubble, with a half-life of 24 to 48 hours and a duration of 5 to 6 days, also has these 2 properties and remains in the eye long enough to carry out its task.

Although some retinal surgeons use pneumatic retinopexy for small or limited detachments only, we routinely attempt the procedure in all patients with RRD—even those with total detachments—as long as they meet the eligibility criteria. Our clinical experience is that pneumatic retinopexy works well.

Reattachment failure occurs for 2 main reasons: (1) persistent vitreous traction on the break such that the buoyancy of the bubble fails to close the break and (2) development of new or sequential breaks, presumably secondary to vitreous traction that is promoted by a bubble. In this study, the incidence of new or missed breaks in the C_3F_8 gas group (12.7%) was comparable to that reported in previous studies (11.7%).¹⁸ The C_3F_8 gas group had a much higher rate of new or missed breaks (compared with 4.8% for the air group), which may be attributed to a greater vitreous traction effect caused by the progressive expansile gas.

As we noted, reattachments in 3 patients in the air group and 8 in the C_3F_8 gas group failed because of a new or missed break. The remaining failures (22 in the air group and 9 in the C_3F_8 gas group) were attributed to too much residual vitreous traction, which allowed the break to flatten or caused a reopening despite chorioretinal adhesion.

Our study is the first, to our knowledge, to directly compare air and C_3F_8 gas in a double-blind, randomized, controlled trial. Furthermore, the number of patients who were lost to follow-up after randomization was minimal. However, we controlled this problem with a sensitivity analysis in which the assumed best (all attached) or worst (all detached) did not change the result of the primary outcome. All these factors strengthen the validity of our conclusions.

The one limitation of this study was the blinding. Although the patients, those administering the intervention, and those assessing the outcomes were unaware of the group assignment, the assessor could determine that

air had been administered because it was reabsorbed faster than expansile gas. The assessor, therefore, might have had selection bias for repeated injections. The crossover also might have biased the study toward equivalency. In those cases, we used both intention-to-treat and per-protocol methods for analysis. The similar results increase the confidence in our conclusions.

In summary, pneumatic retinopexy using air is associated with a nonsignificantly lower initial reattachment rate than is pneumatic retinopexy using C₃F₈ gas but results in an equivalent final reattachment rate and final visual recovery. We recommend using either filtered air or C₃F₈ when treating RRD by pneumatic retinopexy.

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100 Years Ago in the Archives

In the various discussions which have taken place, from time to time, as to the advantages and disadvantages of this operation, it has been contended, by the opponents of the operation for the extraction of the cataract in the capsule, that one of the chief objections to this operation is the frequency of the escape of vitreous. This being the only complication which is at all frequent, and the one which is most commonly met with beginners in this operation, I inquired from Major Smith on my arrival in Jullundur in 1906 if any series of cases had ever been published, in which the after-effects of escape of vitreous in this operation were given.

Reference: Lister AEJ. The after-effects of escape of the vitreous during the operation of extraction of cataract in the capsule, by Smith's operation. *Arch Ophthalmol*. 1910;39:1.

RESEARCH ARTICLE

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Caesarean section without medical indications is associated with an increased risk of adverse short-term maternal outcomes: the 2004-2008 WHO Global Survey on Maternal and Perinatal Health

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Abstract

Background: There is worldwide debate about the appropriateness of caesarean sections performed without medical indications. In this analysis, we aim to further investigate the relationship between caesarean section without medical indication and severe maternal outcomes.

Methods: This is a multicountry, facility-based survey that used a stratified multistage cluster sampling design to obtain a sample of countries and health institutions worldwide. A total of 24 countries and 373 health facilities participated in this study. Data collection took place during 2004 and 2005 in Africa and the Americas and during 2007 and 2008 in Asia. All women giving birth at the facility during the study period were included and had their medical records reviewed before discharge from the hospital. Univariate and multilevel analysis were performed to study the association between each group's mode of delivery and the severe maternal and perinatal outcome.

Results: A total of 286,565 deliveries were analysed. The overall caesarean section rate was 25.7% and a total of 1.0 percent of all deliveries were caesarean sections without medical indications, either due to maternal request or in the absence of other recorded indications. Compared to spontaneous vaginal delivery, all other modes of delivery presented an association with the increased risk of death, admission to ICU, blood transfusion and hysterectomy, including antepartum caesarean section without medical indications (Adjusted Odds Ratio (Adj OR), 5.93, 95% Confidence Interval (95% CI), 3.88 to 9.05) and intrapartum caesarean section without medical indications (Adj OR, 14.29, 95% CI, 10.91 to 18.72). In addition, this association is stronger in Africa, compared to Asia and Latin America.

Conclusions: Caesarean sections were associated with an intrinsic risk of increased severe maternal outcomes. We conclude that caesarean sections should be performed when a clear benefit is anticipated, a benefit that might compensate for the higher costs and additional risks associated with this operation.

Background

Caesarean sections performed appropriately and following an appropriate medical indication are potentially life-saving procedures. In this context, the provision of timely and safe caesarean sections in high maternal mortality countries is a major challenge faced by local health systems [1]. At the same time, in many settings,

women are increasingly undergoing caesarean sections without any medical indication which may contribute to the worldwide secular trend towards higher rates of caesarean sections [2,3]. Over the last two decades, there has been a debate about the appropriateness of caesarean sections performed due to maternal request or following the indication of health care professionals but without a clear medical reason for this surgical procedure. Safety, costs, women's rights and wishes, maternal and professional satisfaction have been elements of this debate [4-10].

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One factor that certainly favoured the liberalization of caesarean section in clinical practice has been the perception of caesarean section as a generally safe procedure, despite the increased costs associated with it. However, the assessment of the intrinsic risk of caesarean sections is complicated by substantial limitations in the existing medical literature [11,12]. Strong evidence would be provided by a well-designed randomized controlled trial, in which healthy women without co-existing medical conditions would be allocated to either intention to deliver by elective caesarean section or expectant management [13]. Obviously, ethical constraints prevent such a trial. In other designs, the scientific community has been struggling with indirectness, imprecision due to sample size limitations and paucity of data, or difficulties in disentangling confounders and effect modifiers in order to establish clear associations between caesarean sections and the occurrence of severe maternal outcomes.

In this context, the World Health Organization Global Survey on Maternal and Perinatal Health (WHOGS) provides evidence on the relationship between mode of delivery and maternal and perinatal outcomes. The WHOGS is a large cross-sectional study conducted in 24 countries around the world between 2004 and 2008. The project has been implemented in three continental steps, and each continental analysis has shown an association between caesarean section and an increased risk of adverse maternal outcomes [5-7,14,15]. In the present three continental analyses we aimed to further investigate the relationship between caesarean section and severe maternal outcomes; more specifically, we wanted to assess the intrinsic risk of caesarean sections with a special focus on those without medical indication.

Methods

Study design

Methodological details of the global survey have been published elsewhere [14]. Briefly, this is a multicountry, facility-based survey that collected data for all delivering women in randomly selected facilities from randomly selected countries. A stratified multistage cluster sampling design was used to obtain a sample from countries and health institutions worldwide. Countries in the WHO regions were further grouped according to adult and under-five infant mortality. From each of these sub regions, four countries were selected, with probability proportional to population size. A total of 54 countries were selected, but owing to financial and practical constraints, the study was implemented in the selected countries of three continents: Africa, the Americas and Asia. For the same reasons, developed countries were excluded (unless they volunteered to participate with their own funds, for example, Japan). Few other countries

(for example, the Democratic People's Republic of Korea, Ethiopia, Haiti, Indonesia) could not participate due to country refusal, security issues or other reasons. A total of 24 countries took part in the study. In each country, two regions or provinces, in addition to the capital city, were randomly selected with probability of selection proportional to their size. Once a province had been selected, we obtained a census of all facilities within the province with more than 1,000 births per year and those reported as able to perform caesarean sections. If there were more than seven facilities, seven were randomly selected with probability of selection proportional to the number of births per year. If there were fewer than seven facilities, all were selected. In each of the selected institutions, we studied all women admitted for delivery during three months in institutions with 6,000 or fewer expected deliveries per year and during two months in those with more than 6,000 expected deliveries per year.

Data collection took place during 2004 and 2005 in Africa and the Americas and during 2007 and 2008 in Asia. We obtained written permission from all ministries of health of the participating countries and the directors of the selected facilities. We obtained data for all individuals from medical records and participants were not identified. The Ethics Review Committee of WHO and of each country independently approved the protocol.

Data collection

Data were collected for institutions and for individuals. For institutions, the hospital coordinator completed a form in consultation with the director or head of obstetrics. Data included characteristics of maternal and perinatal care, including the availability of laboratory tests; anesthesiology resources; services for intrapartum care, delivery, and care of the newborn baby; and presence or absence of basic emergency medical and obstetric care facilities, intensive care units (ICUs), and human and training resources. For individuals, data were obtained from women's medical records to complete a two-page form. Individual data included demographic characteristics, maternal risk, current pregnancy, method of delivery, and outcomes (maternal and perinatal) up to hospital discharge. All women giving birth at the facility during the study period were included. Trained staff reviewed medical records of all women and their babies before discharge from the hospital, and abstracted data daily to their forms for individual data collection. The hospital coordinator supervised data collection, resolving or clarifying unclear medical notes before forms were sent for data entry. Attending staff updated incomplete records before discharge. Criteria for data abstraction were defined in the manuals of operations, which were available for staff training and monitoring of data quality, keeping to a minimum the need for judgment and

interpretation. The manual contained definitions of all terms used and synonyms of medical and obstetric terms, and described questions and corresponding answers. Shortly after collection, data were entered at the country, provincial or facility level in a web-based system (MedSciNet AB, Stockholm, Sweden).

Statistical analysis

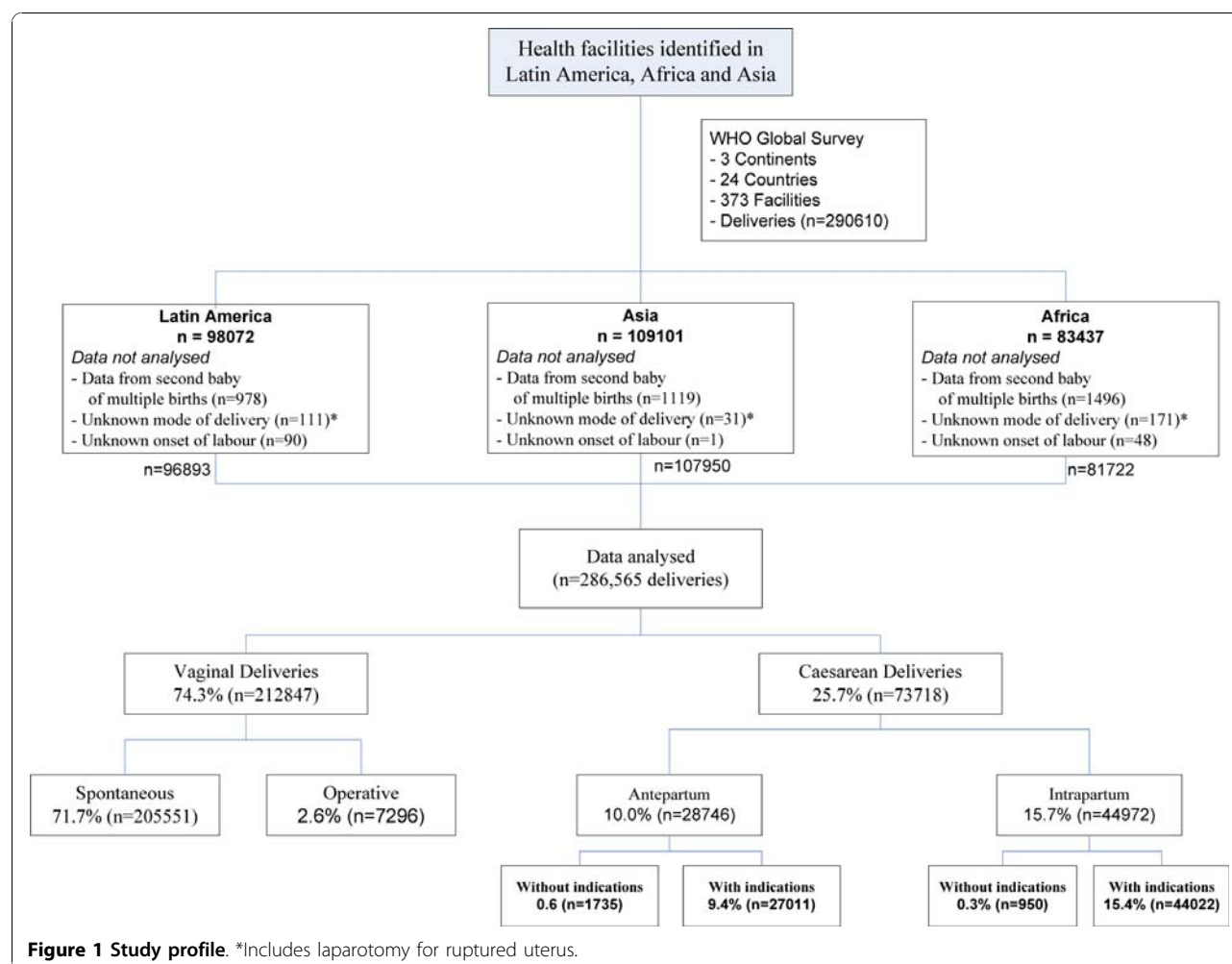
In this three-continent analysis, the continental databases were merged into a global database. Then, frequencies were used to describe modes of delivery for each country and facility characteristics as well as characteristics of mothers and babies for each group's mode of delivery (including caesarean section without medical indication). The main outcome was severe maternal outcome, defined as the occurrence of any of the following conditions: death, admission to ICU, blood transfusion or hysterectomy within the seven days following birth. The severe perinatal outcomes considered were fetal death, neonatal mortality up to hospital discharge limited to the first week of life, and stay of more than or equal to seven days in the neonatal intensive care unit. Univariate analysis followed by generalized linear and latent mixed models (GLLAMM) for multilevel analysis was performed to study the association between each group's mode of delivery and the severe maternal and perinatal outcome using the GLIMMIX procedure in SAS (version 9.1 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina, USA). This procedure was intended to account for clustering effects within facilities and the analysis was adjusted for possible confounding factors and effect modifiers, including individual and institutional characteristics. Among the institutional characteristics, a hospital complexity index was used to assess the hospital capacity in terms of providing essential health services, emergency obstetric care and human resources. This hospital complexity index was used in previous Global Survey analysis and was detailed elsewhere [14]. Risks of maternal and perinatal outcomes associated with modes of delivery (including caesarean section without medical indications) were presented by adjusted Odd Ratios (Adj OR) with corresponding 95% Confidence Intervals (95% CI). Heterogeneity between countries was explored through simple regional stratification and adjusted country-based forest plots. Two subgroup analyses were conducted, one excluding all women with morbidities, complications, multiple pregnancies, breech presentations and previous caesarean sections and another of neonates with breech presentation.

Results

A total of 24 countries and 373 health facilities participated in the WHO Global Survey on Maternal and Perinatal Health, collecting information on 290,610

deliveries. The study was implemented in seven African countries (131 health facilities, 83,437 participants), eight Latin American countries (120 health facilities, 98,072 participants) and nine Asian countries (122 facilities, 109,101 participants). Most of the facilities were located in urban areas ($n = 275$) and of low complexity ($n = 280$). Data from the second or high order baby in multiple pregnancies and from participants with unknown mode of delivery or unknown onset of labour were not analysed, resulting in 286,565 participants included in the present analysis. Figure 1 presents the study profile, while Table 1 shows the total number of deliveries and facilities by country, and percentages of deliveries by mode and country. African countries had the highest rates of spontaneous vaginal delivery while Asian countries tended to have higher rates of operative vaginal delivery. The overall caesarean section rate was 25.7% and the Chinese health facilities had the highest caesarean section rates (average for Chinese health facilities: 46.2%). A total of 1.0 percent of all deliveries had caesarean sections without medical indications, either due to maternal request or in the absence of other recorded indications. In 23 out of 24 countries, the overall proportion of women delivering by caesarean section without medical indication ranged from 0.01 to 2.10%. In the Chinese institutions participating in this survey this figure was exceptionally higher at 11.6%. A total of 63% of all caesarean sections without medical indications were performed in Chinese health facilities ($n = 1,689/2,685$ caesarean sections without medical indications; 11.6% of all deliveries in China). Table 2 presents characteristics of women by mode of delivery. Women delivering by caesarean section antepartum without medical indications had some distinctive features: a higher proportion of married women, fewer adolescents, more educated and more primiparous women, and less frequent antecedent of low birth weight and fetal and neonatal death in a previous pregnancy. A proportion of women having caesarean sections without a medical indication had some other comorbidities, which, nevertheless, were not considered as the indication for the caesarean section.

Table 3 presents the risk of severe maternal outcomes by mode of delivery. Overall, the prevalence of severe maternal outcomes was 37 cases/1,000 deliveries. In addition, compared to spontaneous vaginal delivery, all other modes of delivery presented an association with increased risk of death, admission to ICU, blood transfusion and hysterectomy, including antepartum caesarean section without medical indications (Adjusted Odds Ratio (Adj OR), 5.93, 95% Confidence Interval (95% CI), 3.88 to 9.05) and intrapartum caesarean section without medical indications (Adj OR, 14.29, 95% CI, 10.91 to 18.72). Table 4 presents the stratification of the



combined severe maternal outcomes by region, showing that in all regions there was a trend towards an increased risk associated with caesarean sections without indication. This association is stronger in Africa, compared to Asia and Latin America. The adjusted country level analysis and the resulting country-based forest plots were limited by the low frequency of severe maternal outcomes: in various countries the outcome data (adjusted OR) became zero or non estimable after adjustment for the factors listed at the footnote of Table 3. Overall, the results at the country-level were more imprecise but a trend towards an increased risk has been observed with no country presenting statistically significant results favoring caesarean section. In the subgroup of women without any recorded morbidity including multiple pregnancies, breech presentations and previous caesarean sections, caesarean sections without indications were compared to spontaneous vaginal births. A total of 1,412 women having caesarean sections were compared to 118,742 women having a spontaneous vaginal delivery:

26 women having caesarean sections and 879 women having vaginal deliveries presented severe maternal outcomes (OR = 2.52; 95% CI 1.70 to 3.73).

Table 5 presents the relationship between mode of delivery and severe perinatal outcome. Compared to spontaneous vaginal delivery, operative vaginal delivery, antepartum caesarean section with indications and any intrapartum caesarean section were associated with an increased risk of severe perinatal outcomes. In the subgroup of neonates with breech presentation, caesarean delivery was associated with a reduced risk of severe perinatal outcome (antepartum caesarean section, adj OR = 0.64, 95% CI 0.51 to 0.80; intrapartum caesarean section, adj OR = 0.80, 95% CI 0.66 to 0.97; data not shown in tables).

Discussion

In this paper, the intrinsic risk of caesarean sections was assessed. Caesarean sections were associated with an intrinsic risk for short-term severe maternal outcomes.

Table 1 Total number of deliveries and facilities by country, and the percentages of deliveries by mode and country

	Vaginal Delivery		Caesarean section without indications		Caesarean section with indications		Total deliveries	Total facilities
	Spontaneous	Operative	Antepartum	Intrapartum	Antepartum	Intrapartum		
	%	%	%	%	%	%	n	n
Africa								
Algeria	80.5	5.9	0.04	0.1	5.9	7.5	15,578	18
Angola	97.7	0.8	0.1	0.02	1.0	0.5	6,322	20
D.R. Congo	84.8	2.3	0.1	0.1	1.4	11.4	8,804	21
Kenya	82.9	1.5	0.1	0.5	3.2	11.8	19,968	20
Niger	91.5	3.2	0.02	0.2	0.4	4.8	8,275	11
Nigeria	81.1	4.4	0.1	0.3	3.6	10.5	8,939	21
Uganda	85.4	1.2	0.1	0.3	2.1	10.9	13,836	20
Americas								
Argentina	62.1	2.8	0.2	0.1	17.8	17.0	10,689	14
Brazil	68.5	2.0	0.3	0.2	15.4	13.6	15,129	19
Cuba	61.7	2.7	0.02	0.1	16.6	18.8	12,642	17
Ecuador	59.2	0.5	0.1	0.6	7.8	31.8	12,414	18
Mexico	60.4	1.9	0.1	0.1	15.8	21.8	20,883	21
Nicaragua	69.1	0.1	0.1	0.2	7.7	22.8	5,636	8
Paraguay	57.3	0.8	1.2	0.9	18.1	21.7	3,460	17
Peru	65.4	0.6	0.01	0.0	13.2	20.8	16,040	17
Asia								
Cambodia	77.6	7.7	0.04	0.2	2.6	11.8	5,565	5
China	52.6	1.2	9.3	2.3	19.7	14.9	14,541	21
India	79.4	2.9	0.1	0.2	3.6	13.8	24,682	20
Japan	74.1	6.1	0.1	0.0	13.9	5.9	3,300	10
Nepal	76.0	3.8	0.04	0.1	6.2	14.0	8,489	8
Philippines	78.4	2.8	0.04	0.1	8.0	10.3	13,295	6
Sri Lanka	65.9	3.5	0.5	0.2	20.2	9.8	15,024	14
Thailand	61.6	4.3	0.3	0.1	13.4	20.2	9,745	12
Vietnam	62.2	2.2	0.2	0.8	4.3	30.2	13,309	15
Total	71.7	2.6	0.6	0.3	9.4	15.4	286,565	373

Overall, this risk was higher in African countries than in Asia or Latin America. These findings corroborate the previous WHO Global Survey continental-level analyses [5-7,15] and also provide further evidence for cautioning physicians and patients about issues related with caesarean sections with no medical indications.

Over the years, it has been noted in the medical literature that the interaction between the maternal underlying condition and the caesarean section operation complicates the assessment of caesarean section intrinsic risk. In order to address this issue, we tried to account for the contribution of the medical conditions leading to the operation, other risk factors, confounders and effect modifiers through multilevel statistical modeling. The

results of this statistical adjustment (presented in Table 3) show a substantial positive association between caesarean section and severe maternal outcomes. Similar methods were used in the previous continental analysis for Asia and it is reassuring to find a consistent trend in the two other continents. Furthering this approach, we conducted a subgroup analysis including only women with no identifiable medical risk factors: the caesarean section operation was found to increase the risk of severe maternal outcomes. Stratifying the assessment at continent and country level, similar findings were found. Operative vaginal delivery was also found to be associated with an increased risk of severe maternal outcomes suggesting that these interventions should be

Table 2 Selected maternal characteristics and mode of delivery (%)

	Vaginal delivery		Caesarean section without indications		Caesarean section with indications		Total N = 286,565
	Spontaneous	Operative	Antepartum	Intrapartum	Antepartum	Intrapartum	
	N = 205,551	N = 7,296	N = 1,735	N = 950	N = 27,011	N = 44,022	
Marital status (single)	13.5	9.3	2.7	6.0	11.8	10.7	12.7
Maternal age							
≤16 years	2.5	2	0.1	1.9	1.4	2.4	2.3
16 to 35	87.8	85.7	89.4	85.9	80.1	86	86.8
≥35	9.7	12.3	10.6	12.3	18.5	11.6	10.9
Years of education							
<7	30.9	28.4	11.4	20.5	18.4	24.7	28.6
7 to 12	57.1	54.9	59.0	56.1	59.4	57.6	57.4
>12	12	16.7	29.7	23.4	22.2	17.7	14.1
Primiparous	41.2	57.3	73.3	58.8	37.6	49.7	42.8
Previous pregnancy							
Low birth weight	10.0	14.1	3.1	5.4	14.9	10.1	10.5
Fetal or neonatal death	2.0	2.4	1.6	3.6	2.6	2.6	2.1
Caesarean delivery in the last pregnancy	2	5.9	6.7	11.9	39.3	23.5	9
Current pregnancy							
Induced labour	9.9	15.4	0.0	13.9	0.0	13.9	9.7
Prelabour rupture of membranes	9.4	13.2	8.4	16.0	8.7	15.3	10.3
Pregnancy induced hypertension	2.8	5.3	2.9	3.2	8.5	5.5	3.8
Pre-eclampsia	1.6	3.2	1.3	1.3	8.9	4.8	2.8
Eclampsia	0.2	0.8	0.1	0.3	1	0.6	0.4
Chronic hypertension	0.6	1	0.2	0.2	2.4	1.2	0.8
Vaginal bleeding in second half of pregnancy	0.9	1.2	0.6	0.9	3.6	2	1.3
Suspected fetal growth impairment	0.8	1	0.3	0.7	2.5	1	1
Breech or other non-cephalic presentation	1	25.1	0	0	14.7	12.6	4.7
Referred for complication related to pregnancy	18.8	23.9	9.1	14.2	34	28.8	21.8
HIV	0.8	0.5	0.5	1.4	1	0.9	0.8
Cardiac/Renal diseases	0.3	1	0.5	0.5	1.1	0.5	0.5
Chronic respiratory conditions	0.5	0.7	0.3	0.2	1	0.6	0.6
Diabetes mellitus	0.4	0.7	1.5	0.3	2.6	1	0.7
Malaria	3.3	2.7	0.2	1.3	0.4	1.1	2.6
Sickle cell anaemia	0.3	0.1	0.0	0.3	0.5	0.4	0.3
Severe anaemia	0.5	0.8	0.1	0.5	0.8	0.5	0.6
Pyelonephritis or urinary infection	5.9	4.4	0.6	5.4	8.4	8.6	6.5
Other medical conditions	5.3	5.3	10.2	5.7	12.6	8.2	6.5

performed very carefully by trained providers and only when necessary.

Severe maternal outcomes are relatively rare conditions during pregnancy and childbirth. This factor may contribute to the misperception of safety related to caesarean section and lead to the overuse of the procedure. The relatively low frequency of severe outcomes also makes their appropriate assessment more complex, requiring large databases. The present analysis and findings were possible due to key features of the WHO

Global Survey on Maternal and Perinatal Health project. In this project, standard methods were used across 373 hospitals around the world, generating a consistent and large database, containing a considerable number of severe maternal outcomes, including maternal deaths, intensive care unit admission, blood transfusion and hysterectomy. Another unique feature of the database was the concurrent data collection in all participating health facilities in each region thus ensuring that clinical practice in the various settings was captured during the

Table 3 The relationship between mode of delivery and severe maternal outcomes (that is, death, admission to ICU, blood transfusion, hysterectomy)

Maternal outcomes	n/N (%)	Adjusted OR [95%CI]
Death*		
Spontaneous (reference)	196/205,551 (0.10)	1
Operative	34/7,296 (0.47)	2.9 (1.84 to 4.56)
Antepartum without indications	0/1,735(0)	Not estimated
Intrapartum without indications	2/950(0.21)	3.21 (0.78 to 13.2)
Antepartum with indications	36/27,011(0.13)	1.51 (0.97 to 2.33)
Intrapartum with indications	74/44,022(0.17)	1.7 (1.24 to 2.33)
Admission to ICU**		
Spontaneous (reference)	1,189/205,551 (0.58)	1
Operative	172/7,296 (2.36)	2.27 (1.89 to 2.73)
Antepartum without indications	22/1,735(1.27)	30.75 (18.12 to 52.17)
Intrapartum without indications	67/950(7.05)	58.85 (41.46 to 83.52)
Antepartum with indications	1,741/27,011 (6.45)	63.4 (56.32 to 71.36)
Intrapartum with indications	3,457/44,022 (7.85)	51.3 (46.56 to 56.59)
Blood transfusion†		
Spontaneous (reference)	1,940/205,303 (0.94)	1
Operative	198/7,287 (2.72)	2.11 (1.79 to 2.48)
Antepartum without indications	9/1,735(0.52)	1.79 (0.91 to 3.52)
Intrapartum without indications	18/950(1.89)	3.7 (2.24 to 6.1)
Antepartum with indications	892/26,967(3.31)	3.75 (3.39 to 4.14)
Intrapartum with indications	1,475/43,928 (3.36)	3.85 (3.55 to 4.16)
Hysterectomy††		
Spontaneous (reference)	82/205,299 (0.04)	1
Operative	11/7,278 (0.15)	3.38 (1.73 to 6.59)
Antepartum without indications	0/1,733(0)	Not estimated
Intrapartum without indications	4/949(0.42)	13.53 (4.79 to 38.2)
Antepartum with indications	100/26,916(0.37)	6.11 (4.38 to 8.52)
Intrapartum with indications	118/43,889(0.27)	6.68 (4.91 to 9.09)
Severe Maternal Outcomes†††		
Spontaneous (reference)	3,147/205,551 (1.53)	1
Operative	346/7,296 (4.74)	1.84 (1.62 to 2.1)
Antepartum without indications	28/1,735(1.61)	5.93 (3.88 to 9.05)
Intrapartum without indications	86/950(9.05)	14.29 (10.91 to 18.72)

Table 3 The relationship between mode of delivery and severe maternal outcomes (that is, death, admission to ICU, blood transfusion, hysterectomy) (Continued)

Antepartum with indications	2,452/27011 (9.08)	13.28 (12.3 to 14.34)
Intrapartum with indications	4,523/44,022 (10.27)	12.05 (11.33 to 12.82)

*Total number of years attended school, birth weight, Pregnancy induced hypertension or preeclampsia or eclampsia or chronic hypertension, suspected fetal growth impairment, vaginal bleeding in second half of pregnancy, Breech or other non-cephalic presentation, referred for complication related to pregnancy or delivery, induced labour, HIV positive, Any other medical complication during pregnancy (excluding chronic hypertension) and incentive for caesarean section (no missing data for this outcome).

**Maternal age, total number of years attended school, birth weight, prelabour rupture of membranes, pregnancy induced hypertension or preeclampsia or eclampsia or chronic hypertension, vaginal bleeding in second half of pregnancy, Referred for complication related to pregnancy or delivery, induced labour, HIV positive, any other medical complication during pregnancy (excluding chronic hypertension), incentive for caesarean section and country (no missing data for this outcome).

†Maternal age, total number of years attended school, primiparaous, birth weight, neonatal death or stillbirth, pregnancy induced hypertension or preeclampsia or eclampsia or chronic hypertension, vaginal bleeding in second half of pregnancy, any antenatal antibiotic treatment, referred for complication related to pregnancy or delivery, induced labour, hiv positive, any other medical complication during pregnancy (excluding chronic hypertension), incentive for caesarean section and country (395 participants with missing data for this outcome).

†† Maternal age, Primiparaous, birth weight, vaginal bleeding in second half of pregnancy, referred for complication related to pregnancy or delivery, any other medical complication during pregnancy (excluding chronic hypertension), country and incentive for caesarean section (501 participants with missing data for this outcome).

†††Maternal age, total number of years attended school, birth weight, neonatal death or stillbirth, prelabour rupture of membranes, pregnancy induced hypertension or preeclampsia or eclampsia or chronic hypertension, vaginal bleeding in the second half of pregnancy, any antenatal antibiotic treatment, breech or other non-cephalic presentation, referred for complication related to pregnancy or delivery, induced labour, hiv positive, any other medical complication during pregnancy (excluding chronic hypertension), country and incentive for caesarean section (data available for at least one of the included outcomes for all participants).

Table 4 Relationship between mode of delivery and severe maternal outcomes by continent

Severe Maternal Outcomes	No (%)	Adjusted OR [95% CI]
Africa †		
Spontaneous (reference)	1011/69,364 (1.46)	1 to
Operative	151/2,298 (6.57)	2.58 (2.12-3.15)
Antepartum without indications	14/63(22.22)	71.29 (32.06 to 158.55)
Intrapartum without indications	36/202(17.82)	40.67 (24.56-67.33)
Antepartum with indications	960/2,399 (40.02)	88.61 (74.88 to 104.86)
Intrapartum with indications	1,942/7,396 (26.26)	54.26 (47.81 to 61.59)
Americas††		
Spontaneous (reference)	946/61130 (1.55)	1
Operative	50/1533 (3.26)	2.2 (1.62 to 2.99)

Table 4 Relationship between mode of delivery and severe maternal outcomes by continent (Continued)

Antepartum without indications	6/157(3.82)	1.94 (0.77 to 4.9)
Intrapartum without indications	10/194(5.15)	4 (2.05 to 7.82)
Antepartum with indications	803/13759(5.84)	3.04 (2.71 to 3.41)
Intrapartum with indications	640/20120(3.18)	1.91 (1.71 to 2.13)
Asia^{†††}		
Spontaneous (reference)	1190/75057 (1.59)	1
Operative	145/3465 (4.18)	1.91 (1.56 to 2.35)
Antepartum without indications	8/1515(0.53)	2.14 (1.04 to 4.43)
Intrapartum without indications	40/554(7.22)	12.86 (8.83 to 18.73)
Antepartum with indications	689/10853(6.35)	8.09 (7.12 to 9.18)
Intrapartum with indications	1941/16506 (11.76)	11.61 (10.56 to 12.76)

†Maternal age, Total number of years attended school, Primiparaous, Birth weight, Neonatal death or stillbirth, Caesarean section at last pregnancy, Pregnancy induced hypertension or preeclampsia or eclampsia or chronic hypertension, Suspected fetal growth impairment, Vaginal bleeding in 2nd half of pregnancy, Referred for complication related to pregnancy or delivery, Any other medical complication during pregnancy (excluding chronic hypertension), Country, Incentive for caesarean section.

††Birth weight, Prelabour rupture of membranes, Pregnancy induced hypertension or preeclampsia or eclampsia or chronic hypertension, Vaginal bleeding in 2nd half of pregnancy, Any antenatal antibiotic treatment, Referred for complication related to pregnancy or delivery, Induced labour, HIVPOS, Any other medical complication during pregnancy (excluding chronic hypertension) and Incentive for caesarean section.

††† Maternal age, Total number of years attended school, Primiparous, Birth weight, Neonatal death or stillbirth, Prelabour rupture of membranes, Pregnancy induced hypertension or preeclampsia or eclampsia or chronic hypertension, Vaginal bleeding in 2nd half of pregnancy, Breech or other non-cephalic presentation, Referred for complication related to pregnancy or delivery, HIVPOS, Any other medical complication during pregnancy (excluding chronic hypertension), Country and Complexity of index.

(Differently from the previous Asian specific analysis [7], the severe maternal outcomes included in this analysis are: death, admission to ICU, blood transfusion and hysterectomy).

same period. Quality features of the study also ensured that nearly all deliveries in each health facility during the study period were recorded.

Nevertheless, we should acknowledge some weaknesses of this study. The first one is the study design. This is a cross-sectional study, which *per se* makes this evaluation unable to establish causal relationships between caesarean sections and the maternal outcomes. However, considering the existing constraints in terms of using other designs, we consider this a fair approach to the question. Another point is that our findings may not be country or continent representative; our sample was based on a random selection of countries, regions within countries and health facilities. Doing so, we

simply aimed at avoiding other selection biases, and tried to be inclusive as much as possible, considering the available resources we had. Another issue that should be considered is the disproportionately higher contribution of Chinese health facilities to the group of women undergoing caesarean sections without medical indications. The “country” variable was included in the statistical model used to adjust the findings, reducing both the clustering effect and the role of an individual country’s contribution to the results. On the other hand, in the assessment of caesarean sections with indications, the Chinese facilities’ contribution was not especially prominent and the findings were similar.

The low frequency of events makes the absolute risk associated with caesarean sections low, but even this low risk is substantially higher when compared to spontaneous vaginal deliveries. From the population perspective and considering the frequency with which the procedure is practiced, these findings may be relevant for avoiding the occurrence of severe maternal outcomes, especially in those settings where avoidable caesarean sections are more prevalent.

In this context, one could speculate about the relationship of these findings with the underlying health system and the implication of these results to developed countries. The higher intrinsic risk of caesarean sections observed in Africa compared to Asia and Latin America and the lower intrinsic risk in Latin America compared to Asia could suggest some ecological relationship between the strength of health system, urbanization, facility-based care and development status with the safety of surgical procedures including caesarean section. Data from Japan, the only developed country that took part in the study, could clarify that, but the low number of severe maternal outcomes actually prevented a conclusive assessment by country. Nevertheless, the above mentioned ecological relationship could suggest that in developed settings the intrinsic risk of caesarean sections would be lower compared to less developed settings.

Conclusion

We conclude that caesarean sections should be performed when a clear benefit is anticipated, a benefit that might compensate for the higher costs and additional risks in the context of the specific setting where the operation is taking place. This additional risk should be considered by health care professionals and patients when deciding the mode of delivery. In the end, the main challenge related to caesarean sections is making the best use of this procedure, which is certainly an important resource for the reduction of maternal mortality, but of which overuse may be associated with an increased risk of severe maternal outcomes.

Table 5 Perinatal outcomes among singleton and first child of multiple births by mode of delivery

Perinatal outcomes	n/N (%)	Adjusted OR [95%CI]
Perinatal mortality[†]		
Spontaneous (reference)	3218/205551(1.57)	1
Operative	415/7296(5.69)	3.16 (2.76 to 3.61)
Antepartum without indications	6/1735(0.35)	0.72 (0.26 to 1.97)
Intrapartum without indications	16/950(1.68)	2.41 (1.39 to 4.2)
Antepartum with indications	534/27011(1.98)	1.3 (1.15 to 1.47)
Intrapartum with indications	1081/44022(2.46)	2.01 (1.84 to 2.19)
Fetal death^{††}		
Spontaneous (reference)	1981/205551 (0.96)	1
Operative	291/7296 (3.99)	3.25 (2.79 to 3.79)
Antepartum without indications	3/1735(0.17)	0.48 (0.12 to 1.98)
Intrapartum without indications	11/950(1.16)	2.3 (1.2 to 4.4)
Antepartum with indications	248/27011 (0.92)	0.92 (0.78 to 1.09)
Intrapartum with indications	577/44022 (1.31)	1.6 (1.43 to 1.79)
Early neonatal deaths up to hospital discharge[‡]		
Spontaneous (reference)	1237/203570 (0.61)	1
Operative	124/7005 (1.82)	2.76 (2.19 to 3.47)
Antepartum without indications	3/1732(0.17)	0.88 (0.21 to 3.62)
Intrapartum without indications	5/939(0.53)	2.01 (0.8 to 5.06)
Antepartum with indications	286/26477(1.08)	1.68 (1.42 to 1.98)
Intrapartum with indications	504/43445(1.16)	2.2 (1.94 to 2.5)
Stay for ≥7 days in neonatal intensive care unit^{‡‡}		
Spontaneous (reference)	2704/205551(1.32)	1
Operative	203/7296(2.78)	1.57 (1.31 to 1.88)
Antepartum without indications	17/1735(0.98)	1.18 (0.7 to 1.99)
Intrapartum without indications	16/950(1.68)	2.09 (1.21 to 3.6)
Antepartum with indications	1466/27011(5.43)	2.63 (2.4 to 2.89)
Intrapartum with indications	1625/44022(3.69)	2.77 (2.55 to 3)
Severe perinatal outcome^{‡‡‡}		
Spontaneous (reference)	5820/205551 (2.83)	1
Operative	613/7296 (8.4)	2.33 (2.07 to 2.62)
Antepartum without indications	22/1735(1.27)	1 (0.61 to 1.62)
Intrapartum without indications	32/950(3.37)	2.48 (1.66 to 3.69)
Antepartum with indications	1968/27011(7.29)	2.05 (1.9 to 2.22)
Intrapartum with indications	2656/44022(6.03)	2.42 (2.27 to 2.58)

[†] Maternal age, Total number of years attended school, birth weight, Neonatal death or stillbirth, Pregnancy induced hypertension or preeclampsia or eclampsia or chronic hypertension, Vaginal bleeding in 2nd half of pregnancy, Any antenatal antibiotic treatment, Referred for complication related to pregnancy or delivery, Induced labour, Any other medical complication during pregnancy (excluding chronic hypertension), country and gestational age.

^{††} Maternal age, Total number of years attended school, birth weight, Neonatal death or stillbirth, Pregnancy induced hypertension or preeclampsia or eclampsia or chronic hypertension, Vaginal bleeding in 2nd half of pregnancy, Referred for complication related to pregnancy or delivery, Any other medical complication during pregnancy (excluding chronic hypertension) and gestational age.

[‡] Total number of years attended school, birth weight, Neonatal death or stillbirth, Vaginal bleeding in 2nd half of pregnancy, Referred for complication related to pregnancy or delivery, Induced labour, country and gestational age.

^{‡‡} Maternal age, Total number of years attended school, Primigravida, birth weight, Neonatal death or stillbirth, Caesarean section at last pregnancy, Prelabour rupture of membranes, Pregnancy induced hypertension or preeclampsia or eclampsia or chronic hypertension, Suspected fetal growth impairment, Any antenatal antibiotic treatment, Breech or other non-cephalic presentation, Referred for complication related to pregnancy or delivery, Induced labour, Any other medical complication during pregnancy (excluding chronic hypertension), country, complexity of index and gestational age.

^{‡‡‡} Maternal age, Total number of years attended school, birth weight, Neonatal death or stillbirth, Caesarean section at last pregnancy, Prelabour rupture of membranes, Pregnancy induced hypertension or preeclampsia or eclampsia or chronic hypertension, Suspected fetal growth impairment, Vaginal bleeding in 2nd half of pregnancy, Breech or other non-cephalic presentation, Referred for complication related to pregnancy or delivery, Induced labour, Any other medical complication during pregnancy (excluding chronic hypertension), country, complexity of index and gestational age.

Abbreviations

95% CI: 95% Confidence Interval; Adj OR: Adjusted Odds Ratio; GLIMMIX: procedure for generalized linear mixed models; GLLAMM: generalized linear and latent mixed models; HRP: UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction; ICU: Intensive Care Unit; OR: Odds Ratio; UNDP: United Nations Development Programme; UNFPA: United Nations Population Fund; USAID: United States Agency for International Development; WHO: World Health Organization; WHOGS: World Health Organization Global Survey on Maternal and Perinatal Health.

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Authors' contributions

JPS, AMG, PL and ML conceived this analysis of the WHO Global Survey on Maternal and Newborn Health database. ML carried out the statistical analysis. JPS drafted the manuscript and AMG, PL, ML, GC, BF and PR provided important input on it. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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ภาคผนวกที่ 2

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Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery (Review)

Suwannachat B, Lumbiganon P, Laopaiboon M



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Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery (Review)
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[Intervention review]

Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery

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ABSTRACT

Background

Vacuum extraction is a common technique of assisted vaginal delivery. Traditionally, it has been recommended that the pressure is increased slowly in a stepwise procedure; some have advocated rapid increases in pressure.

Objectives

To assess the efficacy and safety of rapid versus stepwise negative pressure application for assisted vaginal delivery by vacuum extraction.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (March 2008).

Selection criteria

Randomized controlled trials and quasi-randomized controlled trials of rapid compared with stepwise increase in negative pressure application of vacuum extraction.

Data collection and analysis

Two authors independently assessed trial quality and extracted data.

Main results

One trial of 94 women was included. Duration of vacuum procedure was reduced in rapid application group (mean difference -6.10 minutes, 95% confidence interval -8.83 to -3.37). There were no significant differences in detachment rate, degree of perineal tears, Apgar score less than seven at one and five minutes, umbilical venous pH less than 7.2, scalp laceration greater than a quarter, cephalhematoma and number of tractions.

Authors' conclusions

Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery (Review)
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The rapid negative pressure application for vacuum assisted vaginal birth reduces the duration of the procedure whilst there is no evidence of differences in maternal and neonatal outcome. Due to a small number of participants in the single included trial, the evidence is limited and either policy may be employed until further controlled trials provide conclusive evidence of benefit from one or other method.

PLAIN LANGUAGE SUMMARY

Applying negative pressure rapidly or in steps for vacuum extraction assisted vaginal delivery

Assisted vaginal delivery is an important part of obstetric care. Indications for its use include prolonged second stage of labour, actual or potential fetal compromise or distress and to shorten labour. The established method is to grasp the fetal head with obstetric forceps and turn and position the head to facilitate the descent and birth of the infant. A vacuum extractor is becoming the method of choice as it is less likely to injure the mother although failure of attempted vacuum extraction may occur more often than with forceps. The vacuum extractor is contraindicated with face, brow or breech presentation and if the gestational age of the fetus is less than 34 weeks because of the risk of damage to the scalp (cephalhematoma) and intracranial bleeding.

The pressure for vacuum extraction can be increased in a stepwise procedure, to ensure attachment, or more rapidly. Rapid application would address the concern that vacuum extraction is too slow to be used when rapid delivery is required. Potential adverse effects of rapid application include detachment of the cup and injury of the infants scalp and blood vessels. Only one good quality randomised controlled trial involving 94 women was identified. Rapid negative pressure application for vacuum assisted vaginal birth reduced the duration of the procedure without any evidence of differences in outcomes for the mother or infant. Rapid application reduced procedure time by some six minutes (range 8.8 to 3.4 minutes). Rate of detachment of the cup, degree of perineal tears, low Apgar scores, acidic umbilical cord venous blood, damage to the scalp and number of tractions were not clearly different with rapid and stepwise negative pressure application for vacuum extraction assisted vaginal delivery. The small number of participants in the single included trial means that the evidence is limited.

BACKGROUND

Historically, obstetricians sought a method to assist vaginal delivery, to grasp the fetal head in order to turn and manipulate its position, and facilitate its descent and delivery. Assisted vaginal delivery has become an integral part of obstetric care; the obstetric forceps was the primary instrument used in assisting vaginal delivery. However, more recently, forceps have been overtaken in popularity in some countries by the vacuum extractor (Bofill 1996). In the United Kingdom, there has been an increasing use of vacuum extraction compared with forceps extraction (O'Connell 2000; Patel 2004). The acceptance of the vacuum device as a safe alternative to forceps was delayed in the USA as compared to European countries, but as of 1992, the rate of vacuum delivery surpassed the rate of forceps delivery in the USA (Mikovsky 2001). Rates of vacuum extraction vary around 10% in the Middle East and Canada (Cargill 2004; Shihadeh 2001), 6% in Australia (Laws 2005) and 8% in the USA (Kozak 2002).

Vacuum extraction is fast becoming the method of choice for many assisted vaginal deliveries. Current evidence suggests that when assisted vaginal delivery is required, the vacuum extraction should often be chosen first; principally because it is significantly less likely to injure the mother (Chalmers 1989; Johanson 1999), though failure of attempted vacuum extraction will occur more

often than failed forceps delivery (Johanson 1999).

Indications for vacuum assisted delivery include prolonged second stage of labour, suspicion of actual or potential fetal compromise, and to shorten the second stage of labour for maternal benefit (ACOG 2000). The vacuum extractor is contraindicated with face, brow or breech presentation. It has been suggested that it should not be used at gestations of less than 34 weeks because of the risk of cephalhematoma and intracranial haemorrhage (RCOG 2005; Vacca 1999).

There is a traditional recommendation that, for vacuum cup application, the operator should gradually increase negative pressure at 0.2 kg/cm² every two minutes, to reach 0.8 kg/cm² over 8 to 10 minutes. Theoretically, this process would allow the vacuum to be firmly attached to the fetal head, thus decreasing the chance of vacuum extraction failure (Malmstrom 1965). However, some experts suggest that this is both unnecessary and wastes time (Wider 1967). More recently, it has been suggested that there is no significant difference in the traction force developed between stepwise and rapid application of the vacuum (Svenningsen 1987). Since adequate chignon forms within one to two minutes of creating the vacuum and traction may be commenced after one minute without compromising efficiency and safety (Guardino 1962; Lim 1997; Wider 1967). It has been proposed that, for the soft cups,

negative pressure could be increased to 0.8 kg/cm² in as little as one minute (Kuit 1993). Potential adverse effects of rapid application of vacuum extraction include cup detachment and injury of the fetal scalp and blood vessels.

The perception that vacuum extraction is too slow to be used when rapid delivery is required (e.g. severe fetal distress) may not, therefore, be supportable. In some countries, most obstetricians still use the stepwise negative pressure application, in the belief that this prevents cup detachment. We systematically evaluated whether there are any differences in efficacy and safety in rapid versus stepwise negative pressure application for vacuum assisted vaginal delivery.

Readers may wish to refer to the following Cochrane systematic review for further information on vacuum extraction for assisted vaginal deliveries: 'Vacuum extraction versus forceps for assisted vaginal delivery' (Johanson 1999). This review is currently being updated.

OBJECTIVES

To assess efficacy and safety of rapid versus stepwise negative pressure application for assisted vaginal delivery by vacuum extraction.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials and quasi-randomized controlled trials.

Types of participants

Women undergoing vacuum extraction assisted vaginal delivery.

Types of interventions

Rapid (within two minutes) versus stepwise (as defined by trialists) negative pressure application for vacuum extraction assisted vaginal delivery.

Types of outcome measures

Primary outcomes

(1) Maternal

1. Success or failure rate of vacuum procedure
2. Detachment rate
3. Duration of vacuum extraction procedure

4. Birth passage injury including degree of perineal tears, cervical and uterine tears
5. Actual mode of delivery

(2) Fetal

1. Birth asphyxia (according to trialists' definition)
2. Fetal injury including scalp abrasions or lacerations, caput succedaneum, cephalhematoma, subgaleal hemorrhage, intracranial injury (rely on trialists' definition)
3. Hyperbilirubinemia

Secondary outcomes

(1) Maternal

1. Perineal pain after delivery
2. Perineal wound infection
3. Rectovaginal fistula
4. Postpartum haemorrhage

(2) Fetal

1. Retinal hemorrhage
2. Breastfeeding failure
3. Perinatal death

(3) Obstetrician satisfaction

(4) Maternal satisfaction

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Groups Trials Register by contacting the Trials Search Co-ordinator (March 2008).

The Cochrane Pregnancy and Childbirth Groups 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. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, 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

Selection of studies

Two authors assessed for inclusion all potential studies we identified as a result of the search strategy. There were no disagreements.

Assessment of methodological quality of included studies

Two authors assessed the validity of the identified study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2005). We have described the methods used for generation of the randomization sequence in the 'Characteristics of included studies' table.

(1) Selection bias (allocation concealment)

We assigned a quality score using the following criteria:

- (A) adequate concealment of allocation: such as telephone randomization, consecutively-numbered, sealed opaque envelopes;
- (B) unclear whether adequate concealment of allocation: such as list or table used, sealed envelopes or study does not report any concealment approach;
- (C) inadequate concealment of allocation: such as open list of random-number tables, use of case record numbers, dates of birth or days of the week.

(2) Attrition bias (loss of participants, e.g. discharge very soon after birth, withdrawals, dropouts, protocol deviations)

We assessed completeness to follow up using the following criteria:

- (A) less than 5% loss of participants;
- (B) 5% to 9.9% loss of participants;
- (C) 10% to 19.9% loss of participants;
- (D) more than 20% loss of participants.

(3) Detection bias (blinding of outcome assessment)

We assessed detection bias using the following criteria:

- (A) adequate blinding explanation: such as investigators measured birth passage injury among the women without awareness of the interventions they received;
- (B) unclear blinding explanation: such as investigators measured birth passage injury among the women similarly;
- (C) inadequate blinding explanation: such as birth passage injury was measured from the women in both groups.

The one identified and included trial scored an A when rating selection bias and detection bias.

Data extraction and management

We used the Cochrane Pregnancy and Childbirth Group's data extraction form template to extract data. Two review authors extracted the data using the agreed form. There were no discrepancies. We used the Review Manager software (RevMan 2003) to enter data.

Data analysis

We carried out statistical analysis using RevMan 2003. Where relevant, we reported birth passage injury, postpartum haemorrhage, birth asphyxia, fetal injury and other binary outcomes using risk ratio with 95% confidence intervals.

If we had identified more than one trial or if we identify other trials in future updates, we will use the methods we prespecified in the published protocol - see Appendix 1.

RESULTS

Description of studies

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

We identified two studies as potentially eligible for inclusion in this review. We excluded one study because it was neither a randomized controlled trial nor a quasi-randomized controlled trials (Svenningsen 1987) - see table of 'Characteristics of excluded studies'. A single trial of 94 women met the selection criteria (Lim 1997) - see table of 'Characteristics of included studies' for full details.

Risk of bias in included studies

The one included study was of good quality. Women eligible for the study were randomized to rapid and stepwise method application by using sealed envelopes in blocks of 10. The outcome variables were recorded by the obstetrician one hour after birth between the third and the fifth day after birth; a physical examination of the infant was performed by a paediatrician who paid attention to possible neonatal morbidity associated with ventouse extraction procedures. The paediatrician was not aware of the manner in which the vacuum had been applied. This implies that there could have been outcome assessment bias on the part of the obstetrician. Follow-up data were available on 73 children. In 21 cases, the parents did not return with their child to the outpatient clinic: 10 in the rapid group and 11 in the stepwise group.

Effects of interventions

In the group of women who received rapid method of vacuum application, there was a significant reduction in the duration of the vacuum extraction procedure (mean difference -6.10 minutes, 95% confidence interval -8.83 to -3.37). There were no significant differences in detachment rate, degree of perineal tears, Apgar score less than seven at one and five minutes, umbilical cord venous blood pH less than 7.2, scalp laceration more than a quarter of the surface, cephalhematoma and number of tractions.

DISCUSSION

The policy of rapid negative pressure application for vacuum assisted vaginal birth seems to reduce the duration of the procedure by about six minutes and that can be useful when rapid delivery is required, whilst no increase in cup detachment, or other maternal and neonatal adverse outcomes. The results should be interpreted with caution due to the paucity of evidence.

AUTHORS' CONCLUSIONS

Implications for practice

The rapid negative pressure application for vacuum assisted vaginal birth may be suitable for use, especially if rapid delivery is required.

Implications for research

There is insufficient evidence from this review to guide clinical practice to use rapid negative pressure application method due to a dearth of trials. Whilst many obstetricians already practice in this way, more research is needed to assess the safety of rapid application for vacuum assisted vaginal delivery.

ACKNOWLEDGEMENTS

We would like to thank the SEA ORCHID project for building capacity in research synthesis, thanks to Prof Jim Neilson, Sonja Henderson and Gill Gyte, Cochrane Pregnancy and Childbirth Group, for supervising the completion of the review.

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) 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]

Lim 1997

Methods	Randomized controlled trial using sealed envelopes in blocks of 10. No pretrial sample size given.
Participants	94 women eligible for the study were those with an uncomplicated singleton pregnancy of more than 37 weeks of gestation, with a cephalic presentation. Instrumental vaginal delivery was indicated due to prolonged second stage of labour (defined as at least 1 hour of active expulsive efforts) without signs of fetal distress. 8% of eligible women were excluded.
Interventions	Ventouse extraction procedures were performed by application to the fetal head of a metal cup

Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery (Review)

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Lim 1997 (Continued)

(Malmstrom, 50 mm) connected to an automatic electric pump (Egnell compact 5, Ameda, Cary, Illinois, USA). The conventional stepwise method consisted of 4 incremental steps of 0-2 kg/cm² every 2 min to obtain a final negative pressure of 0-8 kg/cm². In the rapid method the negative pressure of 0-8 kg/cm² was applied in 1 step. When the final pressure had been achieved, traction was undertaken during uterine contractions and maternal expulsive efforts. If there was detachment of the ventouse cup, it was applied again to the fetal head in the manner indicated by the initial randomization.

Outcomes	Duration of the complete procedure, The number of detachment of the cup, Apgar scores at 1 min and 5 min, and acid-base status of venous cord blood, superficial scalp lesions, cephalhematomas and clinical jaundice, serum bilirubin concentration, Scalp lesions were scored according to the extent of the fetal scalp involved: < 1/4, 1/4 to 3/4 or > 3/4 of the surface. The neurological condition of the child was determined by the Sarnat score, including crying, irritability and feeding problems, and a physical neurological examination. The Sarnat score runs from 0 (normal) to 4 (severe neurological damage).
Notes	Follow-up data were available on 73 children. In 21 cases the parents did not return with their child to the outpatient clinic: 10 in the rapid group and 11 in the stepwise group. Sarnat score < 0 was not prespecified in the protocol for this review. There was no low Sarnat score in either group so RR would not be calculated.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment??	Yes	A - Adequate
min: minutes		
RR: risk ratio		

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

Study	Reason for exclusion
Svenningsen 1987	This study was not a clinical trial.

DATA AND ANALYSES

Comparison 1. Rapid versus stepwise negative pressure application

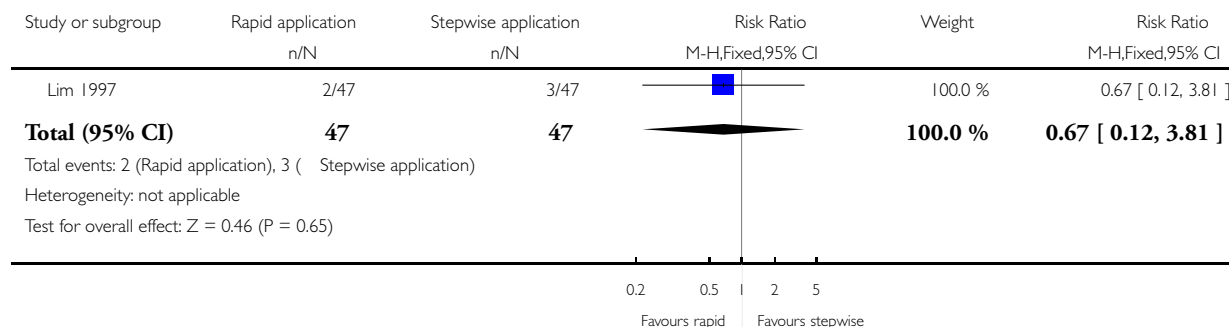
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Success/failure rate of vacuum procedure			Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Detachment rate	1	94	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.12, 3.81]
3 Duration of vacuum extraction procedure	1	94	Mean Difference (IV, Fixed, 95% CI)	-6.10 [-8.83, -3.37]
4 Second degree of perineal tears	1	94	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.24, 2.09]
5 Third degree of perineal tears	1	94	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.06, 15.52]
6 Apgar score < 7 after 1 minute	1	94	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.22, 1.77]
7 Apgar score < 7 after 5 minutes	1	94	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.06, 15.52]
8 Umbilical venous pH < 7.2	1	94	Risk Ratio (M-H, Fixed, 95% CI)	2.01 [0.19, 21.31]
9 Scalp laceration > 1/4	1	73	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.18, 3.03]
10 Cephalhematoma	1	73	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.35, 4.17]
11 Number of traction	1	94	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.55, 0.75]
12 Subgaleal hemorrhage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13 Intracranial injury	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14 Hyperbilirubinemia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15 Perineal pain after delivery	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16 Perineal wound infection	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
17 Rectovaginal fistula	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18 Postpartum haemorrhage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
19 Retinal hemorrhage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
20 Breastfeeding failure	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
21 Perinatal death	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
22 Obstetrician satisfaction	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
23 Maternal satisfaction	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 1.2. Comparison 1 Rapid versus stepwise negative pressure application, Outcome 2 Detachment rate.

Review: Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery

Comparison: 1 Rapid versus stepwise negative pressure application

Outcome: 2 Detachment rate

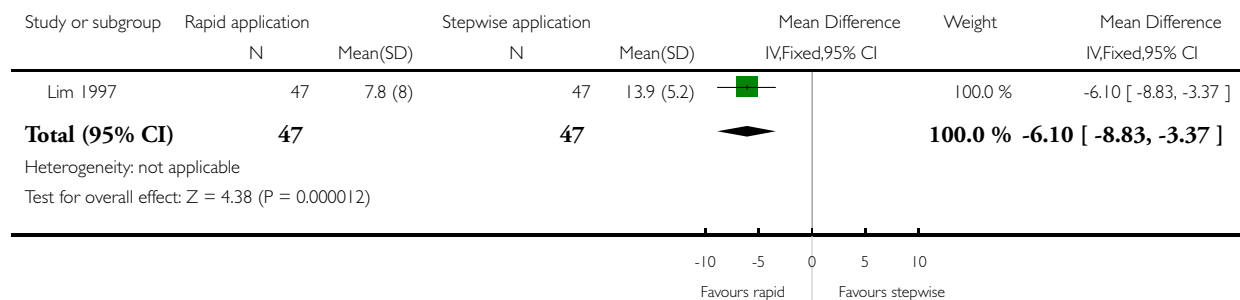


Analysis 1.3. Comparison 1 Rapid versus stepwise negative pressure application, Outcome 3 Duration of vacuum extraction procedure.

Review: Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery

Comparison: 1 Rapid versus stepwise negative pressure application

Outcome: 3 Duration of vacuum extraction procedure

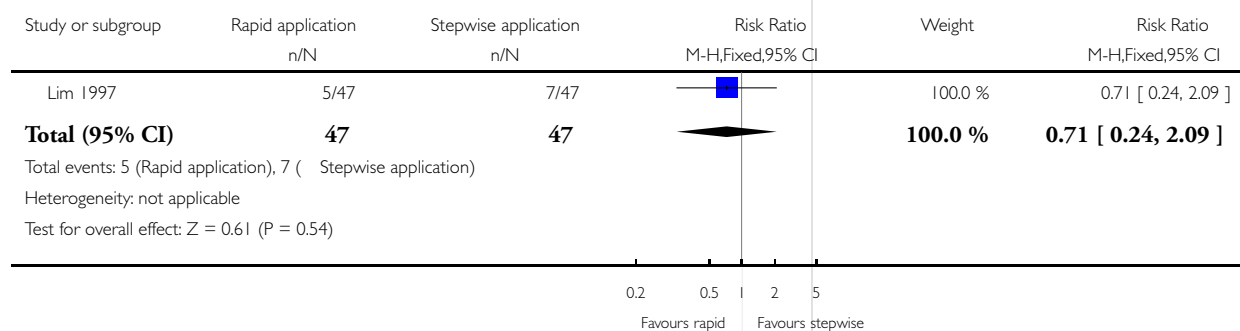


Analysis 1.4. Comparison 1 Rapid versus stepwise negative pressure application, Outcome 4 Second degree of perineal tears.

Review: Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery

Comparison: 1 Rapid versus stepwise negative pressure application

Outcome: 4 Second degree of perineal tears

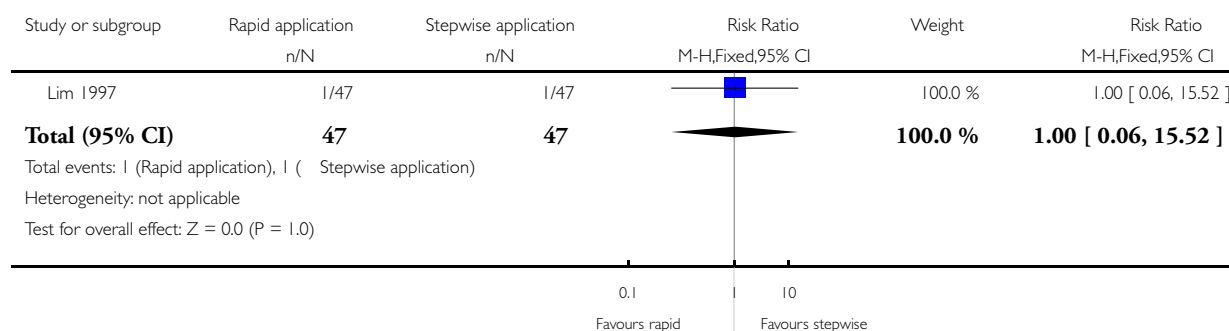


Analysis 1.5. Comparison 1 Rapid versus stepwise negative pressure application, Outcome 5 Third degree of perineal tears.

Review: Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery

Comparison: 1 Rapid versus stepwise negative pressure application

Outcome: 5 Third degree of perineal tears

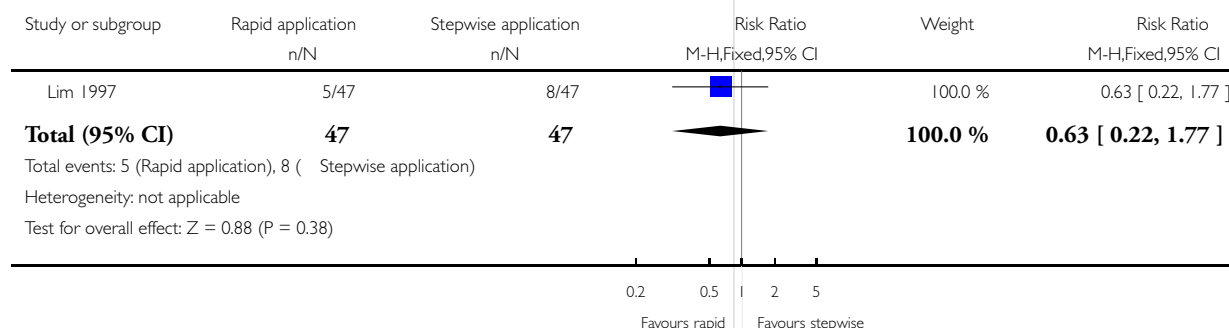


Analysis 1.6. Comparison 1 Rapid versus stepwise negative pressure application, Outcome 6 Apgar score < 7 after 1 minute.

Review: Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery

Comparison: 1 Rapid versus stepwise negative pressure application

Outcome: 6 Apgar score < 7 after 1 minute

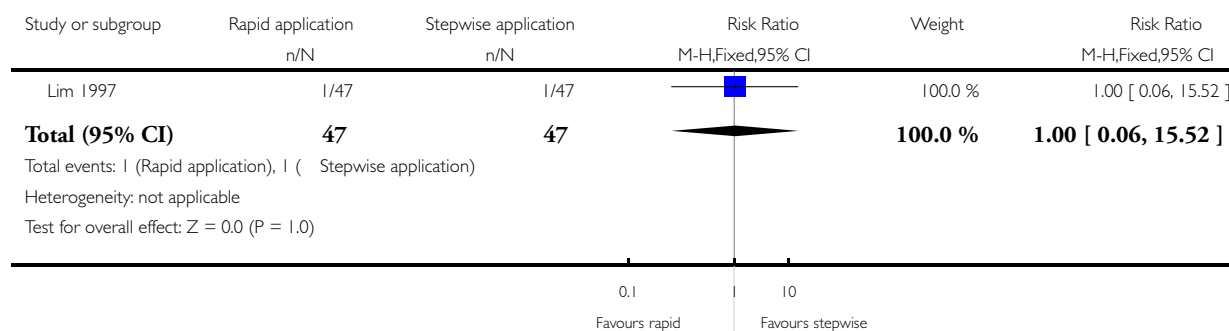


Analysis 1.7. Comparison 1 Rapid versus stepwise negative pressure application, Outcome 7 Apgar score < 7 after 5 minutes.

Review: Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery

Comparison: 1 Rapid versus stepwise negative pressure application

Outcome: 7 Apgar score < 7 after 5 minutes

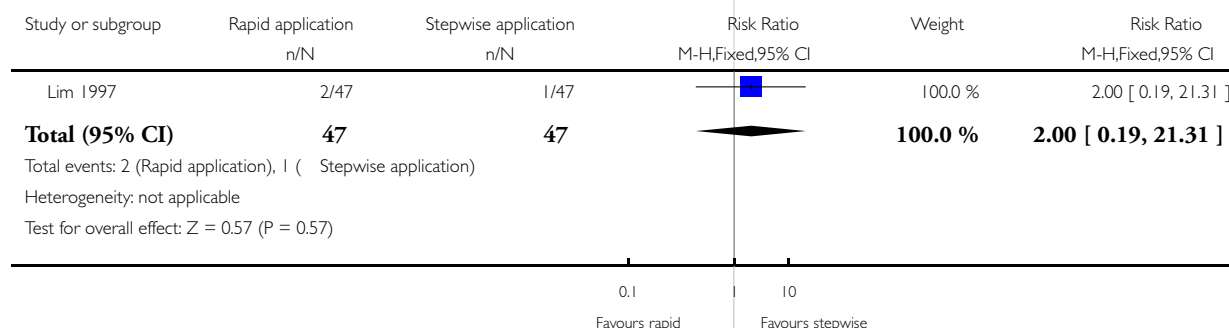


Analysis 1.8. Comparison 1 Rapid versus stepwise negative pressure application, Outcome 8 Umbilical venous pH < 7.2.

Review: Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery

Comparison: 1 Rapid versus stepwise negative pressure application

Outcome: 8 Umbilical venous pH < 7.2

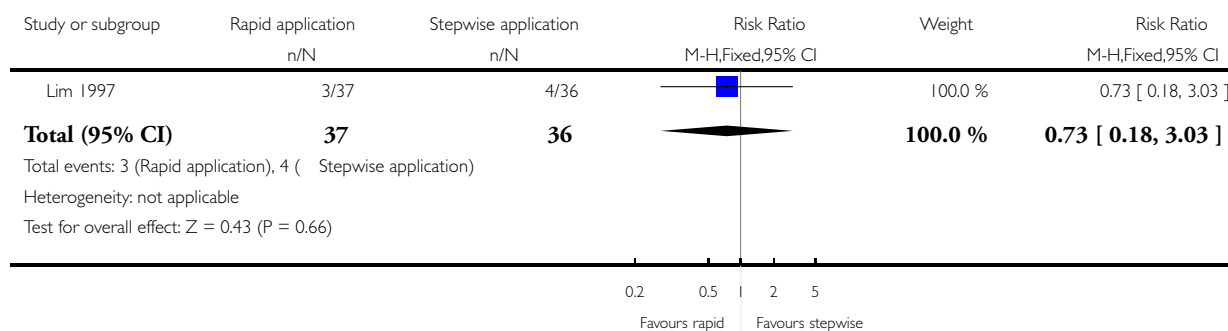


Analysis 1.9. Comparison 1 Rapid versus stepwise negative pressure application, Outcome 9 Scalp laceration > 1/4.

Review: Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery

Comparison: 1 Rapid versus stepwise negative pressure application

Outcome: 9 Scalp laceration > 1/4

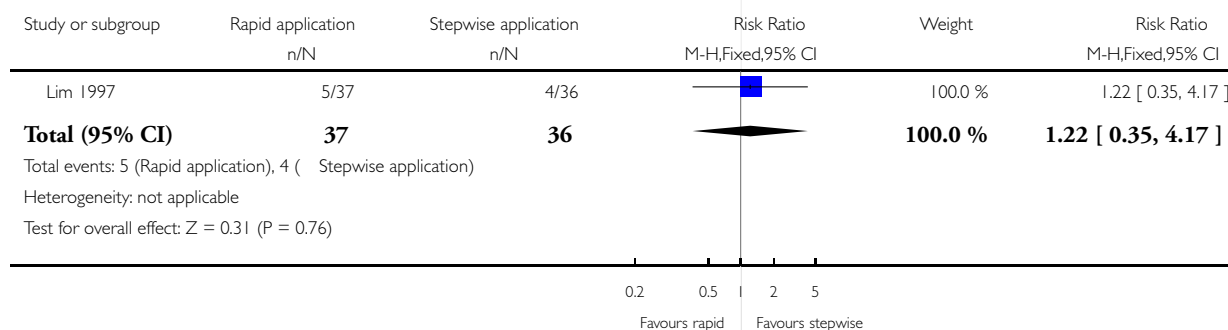


Analysis 1.10. Comparison 1 Rapid versus stepwise negative pressure application, Outcome 10 Cephalhematoma.

Review: Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery

Comparison: 1 Rapid versus stepwise negative pressure application

Outcome: 10 Cephalhematoma

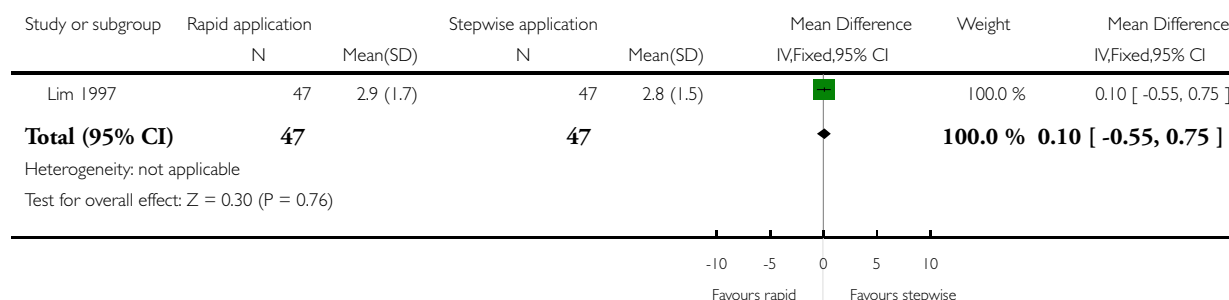


Analysis 1.11. Comparison 1 Rapid versus stepwise negative pressure application, Outcome 11 Number of traction.

Review: Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery

Comparison: 1 Rapid versus stepwise negative pressure application

Outcome: 11 Number of traction



APPENDICES

Appendix 1. Methods to be used if other studies identified

We will use the mean difference to combine trials that measure the same outcome, but use different methods. If there is evidence of skewness, this will be reported.

We will assess heterogeneity by visual forest plots of the outcomes' data among trials and by using the I-squared statistic (Higgins 2005) with 95% confidence interval. If we find statistical heterogeneity among the trials, inconsistent forest plots and I-square exceeding 50%, we will look for an explanation using subgroup analysis. The analysis will be conducted where sufficient data are available according to the following specified factors including type of vacuum extraction procedure (ACOG 2000), type of cup, parity, gestation, indication of delivery, with or without epidural anesthesia. If trials in individual subgroups of the potential factors are thought to be comparable by interaction test as described by Deeks 2001, we will use a random-effects meta-analysis for estimating an overall summary. Alternatively, we will use fixed-effect meta-analysis for combining data.

Where sufficient trials are included, we will consider publication bias using funnel plots of between-treatment effect and its precision of individual trials, and Egger's test (Egger 1997). If we find asymmetry funnel plots with statistical publication bias, we will further examine the effect of the bias on the meta-analysis conclusion using sensitivity analysis.

We will carry out sensitivity analyses to explore the effect of trial quality and, where appropriate, cluster-randomized trials on the meta-analysis conclusion. The trial quality will involve analysis based on high-quality trials. Trials of poor quality will be excluded in the analysis (those rating B, C, or D) in order to assess for any substantive difference to the overall result.

WHAT'S NEW

Last assessed as up-to-date: 30 March 2008

Date	Event	Description
29 April 2008	Amended	Converted to new review format

HISTORY

Protocol first published: Issue 3, 2007

Review first published: Issue 3, 2008

CONTRIBUTIONS OF AUTHORS

B Suwannachat (BS) initiated the topic. BS, P Lumbiganon and M Laopaiboon drafted the protocol. All review authors approved the final version of the protocol.

BS drafted the first version of the review. All review authors approved the final version of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

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

External sources

- Thailand Research Fund, Senior research scholar, Thailand.
- Thailand Cochrane Network, Thailand.

Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media (Review)

Thanaviratananich S, Laopaiboon M, Vatanasapt P



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[Intervention Review]

Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media

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ABSTRACT

Background

Acute otitis media (AOM) is a common problem in children, for which the antibiotic amoxicillin, with or without clavulanate, is frequently prescribed.

Objectives

To compare the effectiveness of one or two daily doses with three or four daily doses of amoxicillin, with or without clavulanate, for the treatment of AOM in children.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2008, issue 1), which contains the Acute Respiratory Infections (ARI) Group's Specialized Register; MEDLINE (January 1950 to March 2008); EMBASE (1974 to March 2008); the Science Citation Index (2001 to March 2008); and NLM Gateway (HSRProj) (March 2008).

Selection criteria

We included studies if they met the following criteria: randomized controlled trials (RCTs) of children aged 12 years or younger with AOM, diagnosed by the following explicit criteria: acute ear pain (otalgia) and inflamed ear drum (confirmed by positive tympanocentesis or tympanogram of type B or C).

Data collection and analysis

We extracted data on treatment outcomes from individual trials. We assessed quality based on selection bias, performance bias, attrition bias and sample size calculation. The quality grading was defined as low risk of bias, moderate risk of bias or high risk of bias. The results were summarized as risk ratio (RR) and 95% confidence intervals (CI).

Main results

We included six studies with 1601 children in the review. Although the clinical cure rates at the end of therapy and at the follow-up periods of each study were shown to be comparable between the two groups, we did not perform pooled data analysis because of moderate to high risk of biases in the included studies. Most of the children were aged 2 months to 12 years. None of the studies had any consistently significant results either for benefit or harm. The outcomes were assessed at the end of therapy (often 10 days) and this may have been too late to measure any differences.

Authors' conclusions

This review showed insufficient evidence to judge whether once or twice daily doses of amoxicillin, with or without clavulanate, were comparable with three or four daily doses for the treatment of AOM. The evidence appears to be biased and therefore no firm conclusions can be drawn.

PLAIN LANGUAGE SUMMARY

Once or twice daily doses compared with three or four daily doses of amoxicillin, with or without clavulanate, for the treatment of acute otitis media in children

Acute otitis media is very common disease in children and may cause pain and hearing loss. Amoxicillin, with or without clavulanate, is the most commonly used antibiotic for the treatment of acute otitis media. Currently one or two daily doses are increasingly used, in preference to three or four times daily doses, to aid compliance. We could not claim that the different dosage schedules have the same effectiveness, as the included studies were biased. To study whether both dosing schedules have the same effectiveness, a good quality equivalence trial is necessary.

BACKGROUND

Description of the condition

Acute otitis media (AOM) is one of the most common diseases in children. During the first six months of life about 48% of infants have one episode of AOM or otitis media with effusion (OME) and about 20% have two or more episodes (Daly 1999). The peak incidence of AOM occurs between 6 and 12 months of age. It has been found that by the end of the first year of life 62.4% of infants have had one or more episodes of AOM and 17.3% have had three or more episodes (Teele 1989). The risk of developing another episode within one month after the onset of the primary infection is estimated at 35% (Carlin 1987).

The common bacterial pathogens of AOM are *Streptococcal pneumoniae* (*S. pneumoniae*), *Haemophilus influenzae* (*H. influenzae*) and *Moraxella catarrhalis* (*M. catarrhalis*) (Jacobs 1998). These bacteria are becoming increasingly resistant to antibiotics (Barnett 1995; Faden 1994; Henderson 1988; Johnson 1996; Kaplan 1995). Systematic reviews have demonstrated that in uncompli-

cated AOM, about 15 children must be treated with antibiotics to prevent one child having some pain after two days (Glasziou 2004) and about eight children must receive antibiotics to avoid one clinical failure (Rosenfeld 2001). A recent study demonstrated that antibiotics seemed to have most benefit in children younger than two years of age with bilateral AOM, and in children with both AOM and otorrhea (Rovers 2006). However, the emergence of multiple-drug resistant strains, particularly *S. pneumoniae*, complicates the management of AOM and increases the risk of treatment failure. Antibiotics are frequently used for AOM in the US (Froom 1997; Glasziou 2004), where it is the most frequent disease that antibiotics are used to treat in outpatients departments (McCaig 1995). In contrast, the national Dutch guidelines recommend that children be treated for symptoms but do not receive antibiotics unless fever or pain persists (Froom 1997).

Description of the intervention

Due to growing bacterial resistance, the Center for Disease Control and the American Academy of Pediatrics promotes the judicious use of antibiotics in the treatment of AOM. Antibiotic therapy remains an appropriate treatment option for most children with AOM because spontaneous cure rates are lower in complicated AOM and AOM secondary to *S. pneumoniae* infection. When amoxicillin, the treatment of choice in AOM, is not effective or not tolerated in children, an alternative antibiotic such as amoxicillin/clavulanate, or second- and third-generation cephalosporins, which can cover beta-lactamase producing bacteria, should be considered (Pichichero 2003).

The effectiveness of antibiotics does not depend solely on their antimicrobial activity against the suspected pathogens, but also on characteristics such as dosage, appropriate dosing intervals, tolerability and palatability, which promote compliance and adherence. A convenient once- or twice-daily dosing schedule increases the likelihood of compliance with a full course of therapy (Leibovitz 2003). The traditional dosing interval for prescribing amoxicillin, with or without clavulanate, is every six to eight hours. These dosing intervals may result in poor compliance especially for children at school or daycare centers, which necessitates the involvement and co-operation of a third person.

How the intervention might work

The length of time that antibiotic serum levels are above the Minimal Inhibitory Concentration (MIC), or time above the MIC, has been demonstrated to be a major determinant in predicting successful clinical outcomes for beta-lactam antimicrobial agents (Cars 1997; Drusano 1997). This finding denotes that the dosing frequency of beta-lactam antimicrobial agents could be reduced by increasing the dose, in order to maximize time above the MIC. An increased dose, instead of three times daily dosing, will enhance compliance (Grob 1992; Urquhart 1992). However, these studies relate to conditions other than otitis media.

Why it is important to do this review

In recent years, an increased dosing interval of amoxicillin, with or without clavulanate, has been more frequently used to treat AOM (AAPS 2004). It is therefore reasonable to assess clinical trials comparing the effectiveness of reduced dosing intervals (one or two daily doses) with traditional dosing intervals (three or four daily doses) of amoxicillin, with or without clavulanate, for the treatment of AOM in children.

OBJECTIVES

To compare the effectiveness of one or two daily doses with three or four daily doses of amoxicillin, with or without clavulanate, for the treatment of AOM in children.

To compare the complication rates and adverse reactions.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) comparing two different dosing intervals of the same intervention, amoxicillin, with or without clavulanate.

Types of participants

Patients aged 12 years or younger, with AOM diagnosed by acute ear pain (otalgia) and an inflamed ear drum (confirmed by positive tympanocentesis or tympanogram of type B or C). (A tympanogram is the print-out of an impedance bridge showing the stiffness or the compliance of the middle ear structures as it varies with changes in pressure within the external ear canal. A type B tympanogram suggests fluid in the middle ear; type C suggests that the pressure within the middle ear is below atmospheric pressure).

Types of interventions

Once or twice daily doses compared with three or four daily doses of amoxicillin, with or without clavulanate.

Types of outcome measures

Primary outcomes

Clinical cure rate at the end of antibiotic therapy (days 7 to 14), in terms of resolution of otalgia, resolution of fever, and bacteriological cure rate, if data are provided.

Secondary outcomes

1. Clinical cure rate during therapy (days two to three), in terms of resolution of otalgia and resolution of fever.
2. Clinical cure rate post-treatment (one to three months), in terms of resolution of middle ear effusion, as determined by tympanometry, assessed only in those who do not have recurrences of AOM after completion of therapy.
3. AOM complications: recurrent AOM (after completion of therapy), acute mastoiditis.

4. Adverse reactions to medication.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2008, issue 1) which contains the Acute Respiratory Infection (ARI) Group's Specialized Register; MEDLINE (January 1950 to March 2008); EMBASE (1974 to March 2008); the Science Citation Index (2001 to March 2008); and NLM Gateway (HSRProj) (March 2008).

The following terms were combined with the Cochrane highly sensitive search strategy for identifying randomized trials in MEDLINE (Lefebvre 2008), run over CENTRAL and MEDLINE and adapted for the other electronic databases.

MEDLINE (OVID)

- 1 exp Otitis Media/
- 2 Otitis Media, Suppurative/
- 3 otitis media.tw.
- 4 AOM.tw.
- 5 1 or 2 or 3 or 4
- 6 exp Amoxicillin/
- 7 amoxicillin.mp.
- 8 amoxycillin.mp.
- 9 6 or 7 or 8
- 10 (singl* or one or once or two or twice).tw.
- 11 ("q.d." or "qd" or "o.d." or "od" or "b.d." or "bd").tw.
- 12 (three or thrice or four).tw.
- 13 ("t.d.s." or "tds" or "q.i.d." or "qid").tw.
- 14 10 or 11
- 15 12 or 13
- 16 14 and 15
- 17 5 and 9 and 16
- 18 randomized controlled trial.pt.
- 19 controlled clinical trial.pt.
- 20 randomized.ab.
- 21 placebo.ab.
- 22 drug therapy.fs.
- 23 randomly.ab.
- 24 trial.ab.
- 25 groups.ab.
- 26 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
- 27 humans.sh.
- 28 26 and 27
- 29 17 and 28

See [Appendix 1](#) for the EMBASE search strategy; [Appendix 2](#) for the Science Citation Index search strategy; and [Appendix 3](#) for

the NLM Gateway search strategy. We applied no language or publication restrictions.

Searching other resources

We checked the reference lists of identified clinical trials and any relevant reviews or meta-analyses. We contacted major pharmaceutical companies that manufacture antibiotics and relevant experts in the field for additional trial information. We contacted the first author of relevant trials if any questions arose.

Data collection and analysis

Selection of studies

Two review authors (ST, PV) retrieved titles and abstracts from the literature search for checking against the inclusion/exclusion criteria and recorded data on a pre-designed screening form. The same review authors independently screened results for each title/abstract and disagreements were resolved by a third review author. If the title or the abstract were unclear then we requested the full text articles.

Data extraction and management

Two review authors (ST, PV) independently reviewed each article and completed data extraction forms. We resolved disagreements through group discussion.

Assessment of risk of bias in included studies

The criteria for the assessment of study quality were 1) random allocation concealment; 2) blinding; 3) follow up and 4) sample size calculation. We graded risk of bias as A (low risk: plausible bias unlikely to seriously alter the result); B (moderate risk: plausible bias that raises some doubt about the result); and C (high risk: plausible bias that seriously weakens confidence in the result).

We assessed the methodological quality of the selected trials using the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2006). The methods used for the generation of the randomization sequence were described for each trial.

1. Selection bias (randomization and allocation concealment).

We assessed the possibility of selection bias for each trial, using the following criteria:

- a. adequate concealment of allocation (such as telephone randomization, consecutively-numbered, sealed opaque envelopes);
- b. unclear whether adequate concealment of allocation (such as list or table used, sealed envelopes, or study did not report any concealment approach);

c. inadequate concealment of allocation (such as open list of random-number tables, use of case record numbers, dates of birth or days of the week, or did not adequately describe the details of concealment of allocation);

d. did not use concealment of allocation.

2. Performance bias (blinding of participants, researchers and outcome assessment).

We assessed performance bias for each trial, using the following criteria:

a. blinding of participants:

yes: patients did not know which intervention they received or placebos were used;

no: patients knew which intervention they received;

unclear: no information;

b. blinding of outcome assessment:

yes: investigators measured the primary outcome among the patients without awareness of the interventions they received or placebos were used);

no: the primary outcome was measured without blinding of the outcome assessors;

unclear: no information or the study did not describe how outcome assessors were blinded.

3. Attrition bias (loss of participants, for example, withdrawals, drop-outs, protocol deviations) (Laupattarakasem 2008):

a. less than 5% loss of participants;

b. 5% to 9.9% loss of participants;

c. 10% to 19.9% loss of participants;

d. more than 20% loss of participants.

4. Sample size calculation:

a. adequate explanation of sample size calculation (all information related to sample size calculation was available);

b. unclear whether the sample size was calculated or no available information;

c. inadequate explanation of sample size calculation (some information related to sample size calculation was available);

d. not calculated.

Low risk of bias was defined as those receiving an 'A' rating for selection bias, attrition bias and sample size calculation, and 'yes' for blinding of participants and outcome assessment.

Moderate risk of bias was defined as those receiving at least one 'B' or 'C' rating for selection bias, attrition bias, sample size calculation, or 'unclear' for blinding of participants or outcome assessment.

High risk of bias was defined as those receiving at least one 'D' or 'no rating' for selection bias, attrition bias, sample size calculation, and blinding of participants or outcome assessment.

Assessment of heterogeneity

When important heterogeneity was suspected from the χ^2 test for heterogeneity (at 10%), or from visual inspection of the results, we investigated this by looking for differences in clinical

and methodological factors between the trials. When concern about heterogeneity persisted, we considered using a random-effects model. We calculated the I^2 statistic to estimate the degree of heterogeneity.

Assessment of reporting biases

We examined publication bias by using funnel plots (Light 1984). When asymmetry was observed, we used the Trim and Fill method to assess the effect of this asymmetry on the conclusions (Duval 2000). When meta-analysis was inappropriate, we drew conclusions from the trials' descriptive elements, methodological quality, the number of trials with consistent findings, the plausibility of the results, the strength of the associations in the primary trials, as well as consensus among the authors. However, we did not produce the funnel plots because there were only six studies.

Data synthesis

Where appropriate, we will perform meta-analyses to pool trial data using Review Manager (RevMan) 5.0 (RevMan 2008) software. The meta-analysis method will be dependent upon the nature of the outcomes. For categorical data (for example, proportion of participants with cure), we will relate the numbers reporting an outcome to the numbers at risk in each group, to derive a risk ratio (RR) and 95% confidence interval (CI). We will show continuous differences between groups in the meta-analysis (for example, pain relief on a visual analogue scale) as a mean difference (MD) and 95% CI. As a general rule, a fixed-effect model will be used for calculations of summary estimates and their 95% CI.

Subgroup analysis and investigation of heterogeneity

We were unable to assess heterogeneity between trials as no trials were combined. We will assess heterogeneity in future updates if appropriate. If we identify high levels of heterogeneity among trials (exceeding 50%) it will be explored by pre-specified subgroup analyses.

Subgroup analyses will be performed and heterogeneity will be investigated on the basis of types of interventions (i.e. amoxicillin alone, amoxicillin with clavulanate) and dosage.

Sensitivity analysis

If there are sufficient trials in future updates, we will carry out sensitivity analyses to explore the effect of trial quality on the review's conclusions. Analysis of trial quality will be based on allocation concealment. Trials with clearly inadequate allocation concealment will be excluded to assess differences on the overall result.

RESULTS

Description of studies

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

Results of the search

The MEDLINE search retrieved 162 studies. However, there were only six studies relevant to the objectives of this review ([Behre 1997](#); [Damrikarnlert 2000](#); [Hoberman 1997](#); [Jacobsson 1993](#); [Murph 1993](#); [Principi 1986](#)). Among the 229 results retrieved by the EMBASE search, six relevant studies were found ([Behre 1997](#); [Damrikarnlert 2000](#); [Hoberman 1997](#); [Jacobsson 1993](#); [Murph 1993](#); [Principi 1986](#)). No study was retrieved by searching the Science Citation Index and HSRProj. Six studies was found in health services research meetings abstract but only one was relevant to the review objectives ([Damrikarnlert 2000](#)). Six out of 172 studies were retrieved from the CENTRAL search ([Behre 1997](#); [Damrikarnlert 2000](#); [Hoberman 1997](#); [Jacobsson 1993](#); [Murph 1993](#); [Principi 1986](#)).

Included studies

We included five studies involving 1601 children ([Behre 1997](#); [Damrikarnlert 2000](#); [Hoberman 1997](#); [Murph 1993](#); [Principi 1986](#)).

Four studies were supported by pharmaceutical funding ([Behre 1997](#); [Damrikarnlert 2000](#); [Hoberman 1997](#); [Principi 1986](#)). Two trials compared amoxicillin without clavulanate ([Murph 1993](#); [Principi 1986](#)) used one and two times daily versus three times daily, while three studies compared the effectiveness of amoxicillin/clavulanate two times versus three times daily ([Behre 1997](#); [Damrikarnlert 2000](#); [Hoberman 1997](#)). Treatment duration was 10 days in four trials ([Behre 1997](#); [Hoberman 1997](#); [Murph 1993](#); [Principi 1986](#)) and 7 to 10 days in one trial ([Damrikarnlert 2000](#)).

Excluded studies

We excluded the study by Jacobsson ([Jacobsson 1993](#)) because it included only recurrent AOM cases or cases that were not responsive to amoxicillin/penicillin or cefaclor, which differed from other studies. In addition, the total daily dosage for amoxicillin was quite low (20 to 33.2 mg/kg/day).

Risk of bias in included studies

The detailed risk of biases and quality of each study is shown in [Table 1](#). We found no study with low risk of bias among the five included trials. Two studies had a moderate risk of bias ([Damrikarnlert 2000](#); [Murph 1993](#)) while the other three studies had a high risk of bias ([Behre 1997](#); [Hoberman 1997](#); [Principi 1986](#)).

Table 1. Quality assessment for individual trial

Trial	Randomisation process	Allocation concealment	Blinded investigators	Blinded patients	Blinded assessors	Drop-outs	Sample size calculation	Overall quality
Behre 1997	Unclear	No (D)	No	No	Unclear	4.8% to 8.2% (B)	A	High risk
Damrikarnlert 2000	Clear	Unclear (B)	No	No	Unclear	11% to 10.7% (C)	A	Moderate risk
Hoberman 1997	Unclear	No (D)	Unclear	No	Unclear	5.2% to 5.6% (B)	A	High risk
Murph 1993	Clear	Unclear (B)	Yes	Yes	Yes	7.7% (B)	B	Moderate risk
Principi 1986	Unclear	No (D)	No	No	Unclear	0% (A)	D	High risk

Allocation

All five studies claimed that they were randomized clinical trials but only two clearly mentioned the method of randomization. One was by a computer generation method (Damrikarnlert 2000) and the other was by generating a table of random numbers (Murph 1993). Three studies did not describe the method of allocation concealment (Behre 1997; Hoberman 1997; Principi 1986) while two studies did not clearly mention allocation concealment (Damrikarnlert 2000; Murph 1993).

Blinding

There was only one study that had a placebo control and the investigator, participants and assessors were blinded to this (Murph 1993). Three studies did not describe the process of blinding the investigators and participants and the blinding of the assessors was not clearly described (Behre 1997; Damrikarnlert 2000; Principi 1986). The study by Hoberman showed an unclear process for blinding the investigators and assessors and there was no evidence of blinding of the patient (Hoberman 1997).

Incomplete outcome data

There was one study with no drop-outs (Principi 1986). Three studies had less than 10% drop-outs (Behre 1997; Hoberman 1997; Murph 1993) and one study had more than 10% drop-outs (Damrikarnlert 2000).

Selective reporting

Four trials assessed the primary outcome at the end of treatment (Behre 1997; Damrikarnlert 2000; Murph 1993; Principi 1986), while Hoberman 1997 assessed the primary outcome at the follow-up visit, days 32 to 38. Thus we used the secondary outcome (clinical response at days 12 to 14) by Hoberman as the primary outcome in this review and vice versa. The secondary outcome of clinical cure was assessed at days 28 (Behre 1997), days 38 to 42 (Damrikarnlert 2000), days 32 to 38 (Hoberman 1997), and days 30, 60 and 90 (Principi 1986), while Murph (Murph 1993) assessed this outcome only at the end of therapy, on days 10 to 14. Other secondary outcomes assessed were adverse events and compliance rates (Behre 1997; Damrikarnlert 2000; Hoberman 1997), recurrence rate (Hoberman 1997), persistent middle ear effusion without signs and symptoms of infection at day 15, recurrence rate and persistence of OME at days 30, 60 and 90, and adverse events (without showing compliance rates) (Principi 1986). The secondary outcomes in Murph 1993 were resolved AOM with middle ear effusion (MEE) at days 10 to 14 and compliance rates. Two trials did not mention whether the analysis was performed based on an intention-to-treat principle or not (Murph 1993; Principi 1986). Two trials were based on intention-to-treat results only (Behre 1997; Damrikarnlert 2000), and only one trial (Hoberman 1997) reported results of the analysis both on an intention-to-treat and per-protocol principle.

Other potential sources of bias

There was no sample size calculation in one study (Principi 1986). Although the rest of the included studies demonstrated sample size calculation, there were no data for estimated cure rate or improvement rate in the study by Murph (Murph 1993).

Effects of interventions

Clinical cure rates at the end of treatment were reported in all trials. However, clinical cure rates at days 28 to 42 were reported only in three trials (Behre 1997; Damrikarnlert 2000; Hoberman 1997). All three of these trials had a moderate risk of bias. There were only two trials that reported the overall event rates (Behre 1997; Damrikarnlert 2000) and four trials reported the compliance rates (Behre 1997; Damrikarnlert 2000; Hoberman 1997; Murph 1993). Since all studies were of moderate (Damrikarnlert 2000; Murph 1993) to high risk (Principi 1986; Behre 1997; Murph 1993) of bias, we did not perform pooled data analysis. Instead, each study was displayed in forest plots (Analysis 1.1; Analysis 1.2; Analysis 1.3; Analysis 1.4; Analysis 1.5; Analysis 1.6; Analysis 1.7; Analysis 1.8). No microbiological studies of middle ear fluid were performed.

Clinical cure at the end of therapy

Five studies involving 1601 participants compared one or two daily doses of amoxicillin, with or without clavulanate, with three daily doses. However, as previously mentioned, we did not perform pooled data meta-analysis.

Clinical cure at follow up (days 28 to 42)

Three trials reported the outcome at days 28 to 42, which showed no difference in clinical cure rate (Behre 1997; Damrikarnlert 2000; Hoberman 1997). However, all of these trials had a moderate risk of bias (grade C).

Adverse events

Two trials reported overall adverse events (Behre 1997; Damrikarnlert 2000) and included 440 and 438 participants in the one or two daily doses and three daily dose groups, respectively. Two trials reported diarrhea events (Behre 1997; Hoberman 1997). Skin adverse events were reported in one trial (Hoberman 1997). Adverse events in each trial were no different between the two dosages of amoxicillin.

Compliance rate

Compliance rates were reported in four trials (Behre 1997; Damrikarnlert 2000; Hoberman 1997; Murph 1993). Only the study by Murph showed that there was a higher compliance in the three times daily dosages of amoxicillin group than in the reduced dosage group, which, due to the small sample size, could have occurred by chance.

Persistent middle ear effusion at follow-up visits

Only one trial reported the persistence of middle ear effusion ([Principi 1986](#)), and showed no statistically significant difference between the two groups at days 30, 60 and 90 with RR 0.93 (95% CI 0.73 to 1.19), 0.98 (95% CI 0.71 to 1.35) and 0.82 (0.54 to 1.25) respectively. This study, however, had a high risk of bias (grade D).

DISCUSSION

Acute otitis media (AOM) is one of the most common infections for which antibacterial agents are prescribed for children in the US ([Rovers 2004](#)). The diagnosis and management of AOM has a significant impact on the health of children, the cost of providing health care, and the use of antibiotics. Although there has been much discussion surrounding the treatment of uncomplicated AOM using antibiotics or observation, antibiotics are still widely used. The first line antibiotic of choice for AOM is amoxicillin, with or without clavulanate ([AAPS 2004](#)). The effectiveness of antibiotics does not depend solely on their antimicrobial activity against the suspected pathogens, but also on factors such as dosage, appropriate dosing intervals, tolerability and palatability. One or two daily doses of oral antibiotics have a higher compliance rate than doses taken three times daily ([Kardas 2007](#); [Pechere 2007](#)).

Summary of main results

This review identified five RCTs reporting clinical outcomes in children treated with one or two daily doses of amoxicillin, with or without clavulanate, compared to three daily doses. No trial used four daily doses. None of the studies reported a clearly significant outcome for benefits or harms. Due to moderate ([Damrikarnlert 2000](#); [Murph 1993](#)) to high risk ([Principi 1986](#); [Behre 1997](#); [Hoberman 1997](#)) of biases among these studies, we did not perform pooled data analysis. The findings did not show statistical difference in the effectiveness of the two different dosages of amoxicillin, with or without clavulanate. We cannot, however, draw conclusions without valid data from good quality studies.

Overall completeness and applicability of evidence

The included studies all showed moderate to high risk of biases, therefore there was not sufficient evidence to demonstrate the effectiveness of one or two daily dosages compared with three or four daily doses of amoxicillin, with or without clavulanate, for the treatment of AOM. This review did not show sufficient evidence that one or two times daily doses of amoxicillin, with or without

clavulanate, had an equal effectiveness as three or four times daily doses for the treatment of AOM.

Quality of the evidence

Moderate to high risk of biases.

Potential biases in the review process

No.

Agreements and disagreements with other studies or reviews

There have been no other published studies or reviews comparing the two dosages of amoxicillin, with or without clavulanate, for the treatment of AOM.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence appears to be biased and therefore we can draw no firm conclusions.

Implications for research

The information provided in the included studies is of limited value due to major problems in the studies, in particular the lack of microbiological data, the lack of stratification of patients in relation to disease severity and prior patient history of AOM, and the inappropriate age range of included patients. More than 90% of AOM cases occur in patients less than two years of age, however, in all of the included studies the age ranges were between two months and 12 years, with few cases less than two years of age. A good quality equivalence or non-inferiority trial should be performed to see whether the treatments are either equally effective or whether a lower dosage scheme is as effective as a higher dosage scheme. Children less than two years of age should also be included in the study and a microbiological study of middle ear fluid should be performed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Behre 1997

Methods	Multicenter, randomized, single-blinded (observer-blinded) controlled trial conducted in 26 centers in Germany, Belgium, Switzerland, the UK and Eire AOM was defined by the visual appearance of the ear drum or presence of middle ear effusion on otoscopy, and the presence of 2 of the following symptoms: ear pain, ear discharge, hearing loss, fever, lethargy, irritability, anorexia, vomiting or diarrhea Analysis was performed based on the intention-to-treat and per protocol principle, however only the intention-to-treat analysis was shown	
Participants	463 AOM children aged 2 to 12 years (231 and 232 children in the 2 and 3 times daily groups, respectively)	
Interventions	10 days with amoxicillin/clavulanate (70/10 mg/kg/day and 60/15 mg/kg/day for the 2 and 3 times daily groups, respectively)	
Outcomes	Primary outcome Clinical cure at days 10 to 17, defined as complete or partial resolution (212/231 (91.8%) versus 210/232 (90.5%) for the 2 and 3 times daily groups, respectively) Secondary outcomes 1. Clinical cure at day 28 (185/231 versus 180/232 in the 2 and 3 times daily groups, respectively) 2. Adverse events (111/231 and 94/232 children in the 2 and 3 times daily groups, respectively) 3. Compliance rate (at least 80%) (192/231 and 269/232 in the 2 and 3 times daily groups, respectively)	
Notes	Supported by SmithKline Beecham Pharmaceuticals Although 34 and 44 children were noted to withdraw from the study, the total number of children at the end of therapy and follow-up visit were the same as at the entry High risk of bias	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	No	The authors did not describe the method of randomization and allocation concealment

Damrikarnlert 2000

Methods	Multicenter, randomized, single-blinded (observer-blinded) trial conducted at 18 centers in Argentina, Brazil, Costa Rica, India, Kenya, Mexico, Morocco, Nigeria, Thailand and Turkey between August 1996 and March 1998 Block of 6 randomization was performed using SAS software. Although analyses using the intention-to-treat and per-protocol principle were planned, only the intention-to-treat principle analysis was shown	
Participants	415 AOM children aged 2 months to 12 years (209 and 206 children in the 2 and 3 times daily groups, respectively). However, 199 and 187 patients were analyzed for primary outcome	

Interventions	7 to 10 days (depending on national prescribing practice) with amoxicillin/clavulanate 45/6.4 mg/kg/day and 40/10 mg/kg/day (2 versus 3 times daily groups, respectively)	
Outcomes	Primary outcome Clinical success at days 7 to 12 (187/199 (94%) versus 175/187 (94.1%) in the 2 and 3 times daily groups, respectively) Secondary outcome 1. Successful clinical response at days 38 to 42 (153/174 (87.9%) versus 168/180 (93.3%) in the 2 and 3 times daily groups, respectively) 2. Adverse events (25/209 (12%) versus 37/206 (18%) in the 2 and 3 times daily groups, respectively) 3. Compliance rate (at least 80%) (173/209 and 173/206 in the 2 and 3 times daily groups, respectively)	
Notes	Supported by Smithkline Beecham Pharmaceuticals. There were many details which were not inappropriate: 1. The definitions of intention-to-treat (ITT) principle and per-protocol for analysis were not appropriate. The ITT principle should be defined as outcome analysis based on the group which was randomized at entry, while the per-protocol analysis should be according to the treatment received in each group 2. 415 patients were randomized to treatment: 209 versus 206 in the 2 and 3 times daily group. Thirty-six patients of 209 (17.2%) and 40 of 206 patients (19.4%) in the 2 and 3 times daily groups, respectively, withdrew during the study. However, the total patients in Table 2 showed that the total number at the end of therapy (days 7 to 12) was 199 and 187 in the 2 and 3 times daily groups, respectively. Table 4 demonstrated that at the end of therapy (days 7 to 12) and follow-up visit (days 38 to 42) the total patients in the 2 times daily group were 198 and 180 respectively, while the total patients in the 3 times daily group were 186 and 174, respectively. This meant that the total patients in Table 2 and 4 did not match the withdrawal rate 3. 54/209 patients (25.8%) and 74/206 patients (35.9%) were excluded from the per-protocol populations because of poor compliance and failure to return for the end of therapy visit within the specified time window Moderate risk of bias	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	The authors stated that following enrolment, study medication was dispensed by the pharmacist or study nurse who instructed the patient's parent or guardian in its administration

Hoberman 1997

Methods	Multicenter, randomized, non-placebo controlled trial conducted at four university-affiliated hospitals and 20 private practices in the US and Canada between January and July 1994 AOM was defined as either presence of purulent otorrhea for less than 24 hours or evidence of middle ear effusion in addition to at least one indicator of acute middle ear inflammation Investigators were blinded to treatment assignments and patients, parents and guardians were asked not to discuss medications or duration of treatment with investigators
Participants	575 children aged 2 months to 12 years were included (287 and 288 in the 2 and 3 times daily groups, respectively)
Interventions	10 days of amoxicillin/clavulanate 40/10 mg/kg/day 2 times daily versus 45/6.4 mg/kg/day 3 times daily
Outcomes	Primary outcome 1. Recurrence (completely resolved or improved, but recurred or worsened thereafter) at days 32 to 38 (51/287 (17.8%), 34/288 (11.8%). Intention-to-treat principle) Secondary outcomes 1. Clinical cure (completely/improved symptoms and signs of AOM at days 12 to 14) (241/287 (84%) versus 229/288 (79.5%). (Intention-to-treat principle) 2. Adverse events: diaper rash (23/287 (8%) versus 30/288 (10.4%)); vomiting (29/287 (10.1%) versus 31/288 (10.8%)); diarrhea (15/287 (5.2%) versus 20/288 (7%)) 3. Compliance rate (257/287(89.5%) versus 246/288 (85.4%))
Notes	Supported by SmithKline Beecham Pharmaceuticals High risk of bias

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	The authors did not mention the methods of randomization and allocation concealment

Murph 1993

Methods	Double-blind, placebo-controlled study. A table of random numbers was used to generate a randomized sequence AOM was defined as evidence on otoscopic assessment of an inflamed tympanic membrane and presence of middle ear effusion
Participants	77 AOM children, aged 7 months to 12 years old, recruited from the Pediatric Child Health Clinic of the University of Iowa Hospitals and Clinics 10/77 (7.7%) children could not be evaluated because failed to return for follow up or withdrew from the study; 33 and 34 children in the once and 3 times daily groups, respectively, were left for the analysis
Interventions	10 days of amoxicillin 40 mg/kg/day once versus 3 times daily
Outcomes	Primary outcome Resolved AOM with or without MEE (27/33 (82%) and 23/24 (68%) for once and 3 times daily) assessed

Murph 1993 (Continued)

	at days 10 to 14 Secondary outcome 1. Resolved AOM with MEE present at days 10 to 14 (13/33 (39%) versus 8/34 (24%)) 2. Compliance rate (at least 80%): 100% for both groups	
Notes	No pharmaceutical industry support Intention-to-treat principle analysis was not mentioned Moderate risk of bias	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	A table of random numbers was used to assign children to one of the two treatment groups but allocation concealment was not clearly mentioned

Principi 1986

Methods	Randomized controlled study conducted in the outpatient ward of the Pediatric Department IV of the University of Milan between October 1984 and 1985 AOM was defined on clinical data (fever or otalgia or both), otoscopic finding of ear drum, and presence of ear effusion shown by tympanograms. Children with spontaneously perforated ear drums were also included only if the ear had been draining for no longer than 12 hours
Participants	55 AOM children in each treatment group (total 110), aged 6 months to 12 years
Interventions	10 days of amoxicillin 60 mg/kg/day 2 or 3 times daily
Outcomes	Primary outcome Clinical cure (normalization of clinical or relief of acute signs and symptoms of AOM) assessed at day 15 (49/55 (89.1%) versus 51/55 (92.7%) for 2 and 3 times daily groups, respectively) Secondary outcome 1. Persistent middle ear effusion without signs and symptoms of infection at day 15 (41/55 (74.5%) versus 40/55 (72.7%)) 2. Clinical cure at days 30, 60 and 90 (cure at day 30, 44/49 (89.8%) versus 51/51 (100%); at day 60, 42/46 (91.3%) versus 49/50 (98%), and at day 90, 42/46 (91.3%) versus 48/49 (98%)) 3. Persistence of otitis media with effusion (at day 30 (34/49 versus 38/51); at day 60 (28/46 versus 31/50); and at day 90 (20/46 versus 26/49))
Notes	Supported in part by a Farmitalia-Carlo Erba SpA Milano grant Intention-to-treat principle analysis was not mentioned Clinical evaluation at 30 days was stated to be performed in all the children who had entered the study (55 children in each group), however only 49 and 51 in the 2 and 3 times daily groups were analyzed High risk of bias
Risk of bias	

Principi 1986 *(Continued)*

Item	Authors' judgement	Description
Allocation concealment?	No	No randomization process and allocation concealment methods were mentioned

AOM: acute otitis media

MEE: middle ear effusion

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

Jacobsson 1993	1. Included only recurrence or cases that were not responsive to amoxicillin/penicillin or cefaclor, which was different from other studies 2. The total daily dosage for amoxicillin was quite low (20 to 33.2 mg/kg/day)
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DATA AND ANALYSES

Comparison 1. Once or twice daily versus thrice daily

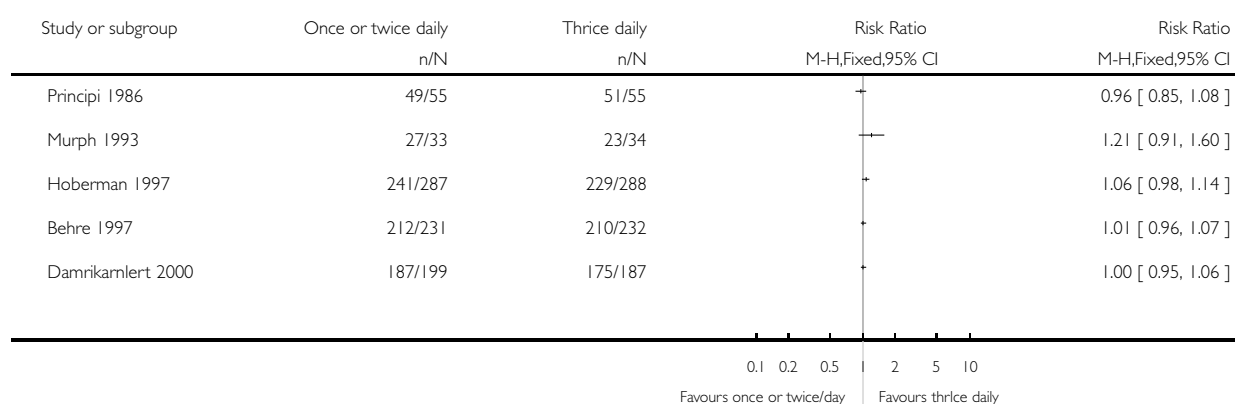
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical cure at the end of therapy	5		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Clinical cure at follow up (days 28 to 42)	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Overall adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Specific adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Diarrhea	2		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2 Skin adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Compliance rate	4		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Persistent middle ear effusion at follow-up visit (day 30)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Persistent middle ear effusion at follow-up visit (day 60)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Persistent middle ear effusion at follow-up visit (day 90)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Once or twice daily versus thrice daily, Outcome 1 Clinical cure at the end of therapy.

Review: Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media

Comparison: 1 Once or twice daily versus thrice daily

Outcome: 1 Clinical cure at the end of therapy

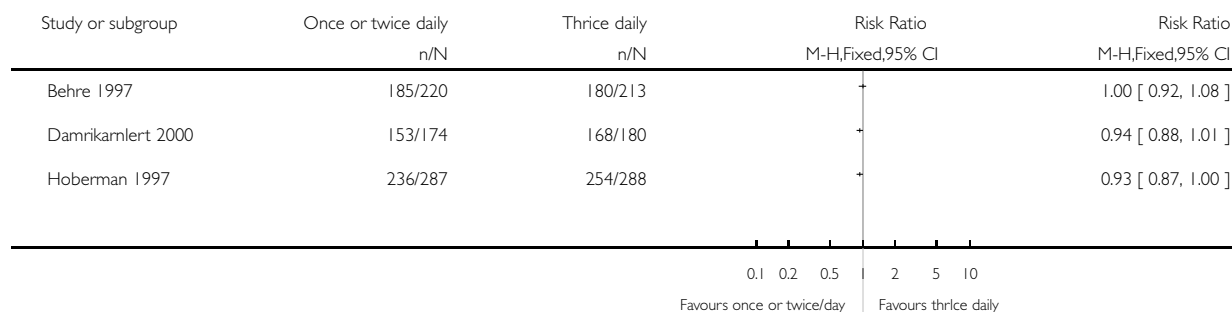


Analysis 1.2. Comparison 1 Once or twice daily versus thrice daily, Outcome 2 Clinical cure at follow up (days 28 to 42).

Review: Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media

Comparison: 1 Once or twice daily versus thrice daily

Outcome: 2 Clinical cure at follow up (days 28 to 42)

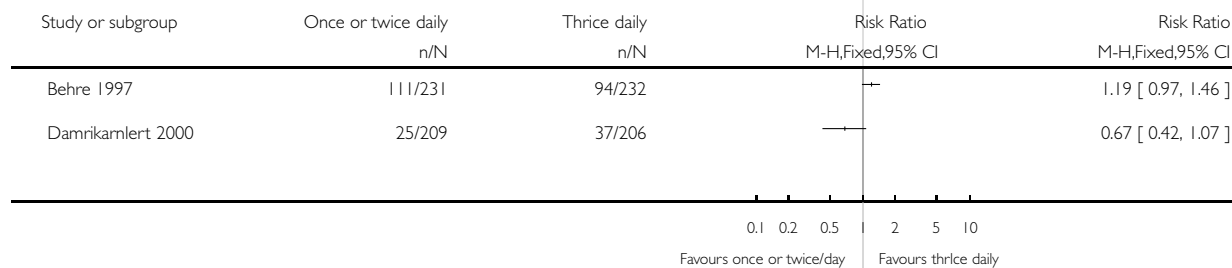


Analysis 1.3. Comparison 1 Once or twice daily versus thrice daily, Outcome 3 Overall adverse events.

Review: Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media

Comparison: 1 Once or twice daily versus thrice daily

Outcome: 3 Overall adverse events

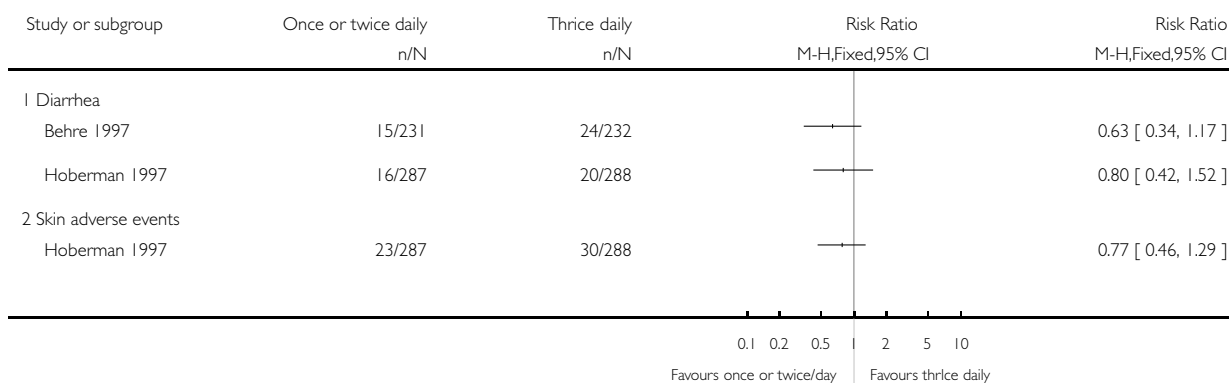


Analysis 1.4. Comparison 1 Once or twice daily versus thrice daily, Outcome 4 Specific adverse events.

Review: Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media

Comparison: 1 Once or twice daily versus thrice daily

Outcome: 4 Specific adverse events

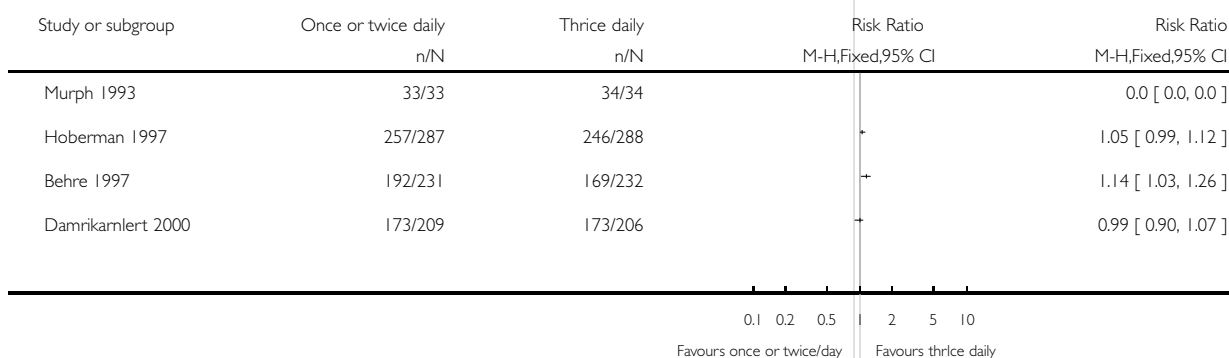


Analysis 1.5. Comparison 1 Once or twice daily versus thrice daily, Outcome 5 Compliance rate.

Review: Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media

Comparison: 1 Once or twice daily versus thrice daily

Outcome: 5 Compliance rate

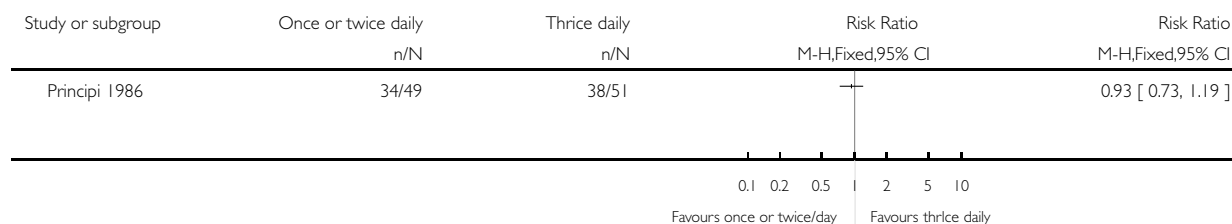


Analysis 1.6. Comparison 1 Once or twice daily versus thrice daily, Outcome 6 Persistent middle ear effusion at follow-up visit (day 30).

Review: Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media

Comparison: 1 Once or twice daily versus thrice daily

Outcome: 6 Persistent middle ear effusion at follow-up visit (day 30)

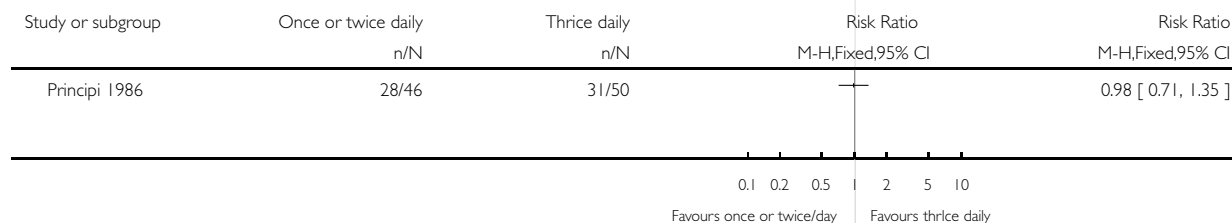


Analysis 1.7. Comparison 1 Once or twice daily versus thrice daily, Outcome 7 Persistent middle ear effusion at follow-up visit (day 60).

Review: Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media

Comparison: 1 Once or twice daily versus thrice daily

Outcome: 7 Persistent middle ear effusion at follow-up visit (day 60)

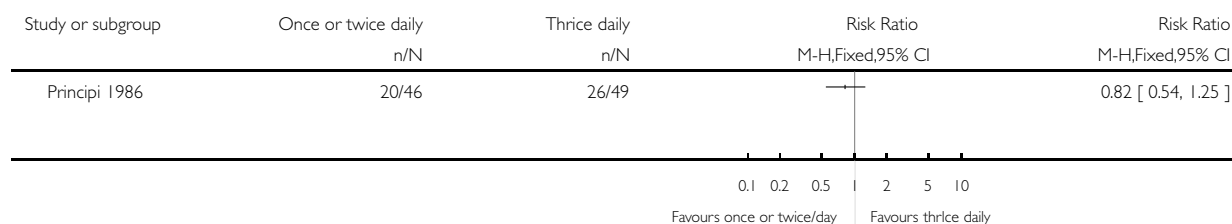


Analysis 1.8. Comparison 1 Once or twice daily versus thrice daily, Outcome 8 Persistent middle ear effusion at follow-up visit (day 90).

Review: Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media

Comparison: 1 Once or twice daily versus thrice daily

Outcome: 8 Persistent middle ear effusion at follow-up visit (day 90)



APPENDICES

Appendix 1. EMBASE search strategy

- #1. 'otitis media'/exp AND [embase]/lim
- #2. 'acute otitis media'/exp AND [embase]/lim
- #3. 'acute suppurative otitis media'/exp AND [embase]/lim
- #4. 'otitis media':ti,ab AND [embase]/lim
- #5. 'aom':ti,ab AND [embase]/lim
- #6. 'asom':ab,ti AND [embase]/lim
- #7. #1 OR #2 OR #3 OR #4 OR #5 OR #6
- #8. 'amoxicillin'/exp AND [embase]/lim
- #9. 'amoxicillin plus clavulanic acid'/exp AND [embase]/lim
- #10. amoxicillin:ti,ab AND [embase]/lim
- #11. amoxycillin:ab,ti AND [embase]/lim
- #12. #8 OR #9 OR #10 OR #11
- #13. (singl*:ti,ab OR one:ti,ab OR once:ti,ab OR two:ti,ab OR twice:ti,ab) AND [embase]/lim
- #14. ('q.d.':ti,ab OR 'qd':ti,ab OR 'o.d.':ti,ab OR 'od.':ti,ab OR 'b.d.':ti,ab OR 'bd':ti,ab) AND [embase]/lim
- #15. (three:ti,ab OR thrice:ti,ab OR four:ti,ab) AND [embase]/lim
- #16. ('t.d.s.':ti,ab OR 'tds':ti,ab OR 'q.i.d.':ti,ab OR 'qid':ti,ab) AND [embase]/lim
- #17. #13 OR #14
- #18. #15 OR #16
- #19. #17 AND #18
- #20. #7 AND #12 AND #19
- #21. 'randomized controlled trial'/exp AND [embase]/lim
- #22. 'controlled study'/exp AND [embase]/lim
- #23. 'single blind procedure'/exp AND [embase]/lim
- #24. 'double blind procedure'/exp AND [embase]/lim
- #25. 'phase 3 clinical trial'/exp AND [embase]/lim
- #26. random*:ab,ti AND [embase]/lim
- #27. placebo*:ti,ab AND [embase]/lim
- #28. 'clinical trial':it AND [embase]/lim
- #29. 'randomized controlled trial':it AND [embase]/lim
- #30. (singl*:ti,ab OR doubl*:ti,ab OR tripl*:ti,ab OR trebl*:ti,ab) AND (blind*:ti,ab OR mask*:ti,ab) AND [embase]/lim

#31. 'controlled clinical trial':ti,ab AND [embase]/lim
 #32. 'controlled clinical trials':ti,ab AND [embase]/lim
 #33. #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR # 31 OR #32
 #34. ('nonhuman'/exp OR 'animals'/exp) NOT 'human'/exp AND [embase]/lim
 #35. #33 NOT #34
 #36. #20 AND #35

Appendix 2. Science Citation Index search strategy

Science Citation Index searched by ISI Web of Knowledge (<http://apps.isiknowledge.com>)

#1 TI = "otitis media"
 #2 TI = amoxicillin
 #3 TI=amoxycillin
 #4 #2 OR #3
 #5 TI = once
 #6 TI = one
 #7 TI = singl*
 #8 TI = two
 #9 TI = twice
 #10 #5 OR #6 OR #7 OR #8 OR #9
 #11 TI = three
 #12 TI=thrice
 #13 TI=four
 #14 #11 OR #12 OR #13
 #15 #10 AND #14
 #16 #1 AND #4 AND 15

Appendix 3. NLM Gateway search strategy

We used the terms ("otitis media" AND (amoxycillin OR amoxicillin) AND (one OR once OR two OR twice OR singl*) AND (thrice OR three OR four) to search NLM Gateway.

WHAT'S NEW

Last assessed as up-to-date: 17 March 2008.

21 January 2010	Amended	Contact details updated.
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HISTORY

Protocol first published: Issue 4, 2004

Review first published: Issue 4, 2008

8 May 2009	Amended	Contact details updated.
18 March 2008	New search has been performed	Searches conducted.
12 March 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Sanguansak Thanaviratananich (ST) was responsible for conceiving, designing and co-ordinating the protocol, developing the search strategy, assessing the quality of studies, entering text into RevMan and writing the review.

Patravoot Vatanasapt (PV) was responsible for designing and co-ordinating the review, assessing the quality of the studies and providing general advice on the review.

Malinee Laopaiboon (ML) was responsible for entering text into RevMan and providing general advice on the statistical analysis and the review generally.

DECLARATIONS OF INTEREST

No conflict of interest known.

SOURCES OF SUPPORT

Internal sources

- Faculty of Medicine, Khon Kaen, Thailand.

External sources

- Thai Cochrane Network, Thailand.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Amoxicillin [*administration & dosage]; Anti-Bacterial Agents [*administration & dosage]; Clavulanic Acid [*administration & dosage]; Drug Administration Schedule; Drug Therapy, Combination; Otitis Media [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Child; Humans

Paracervical local anaesthesia for cervical dilatation and uterine intervention (Review)

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[Intervention Review]

Paracervical local anaesthesia for cervical dilatation and uterine intervention

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ABSTRACT

Background

Cervical dilatation and uterine intervention can be performed under sedation, local or general anaesthesia for obstetrics and gynaecological conditions. Many gynaecologists use paracervical local anaesthesia (PLA) but its effectiveness is unclear.

Objectives

To determine the effectiveness and safety of paracervical anaesthesia for cervical dilatation and uterine intervention when compared with no treatment, placebo, other methods of regional anaesthesia, systemic sedation and analgesia, or general anaesthesia (GA).

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2006, Issue 1), MEDLINE (1966 to January 2006), EMBASE (1980 to January 2006) and reference lists of articles.

Selection criteria

We included randomized or controlled clinical studies involving cervical dilatation and uterine intervention for obstetric and gynaecological conditions.

Data collection and analysis

Two authors independently evaluated studies, extracted data, checked and entered data into Review Manager.

Main results

We included 17 studies involving 1855 participants. No study of PLA versus GA met our criteria; eight studies compared PLA versus placebo. Injection of local anaesthetic was slightly less painful than injection of saline placebo, a reduction of 0.87 points (95% CI 0.14 to 1.60) on a 10-point pain scale. Compared to placebo, PLA reduced abdominal pain during uterine intervention equivalent to two or three points on a 10-point pain scale and reduced the risk of severe pain (RR 0.16, 95% CI 0.06 to 0.74). There was no

evidence that PLA reduced pain after the uterine intervention and little evidence for any effect on postoperative back or shoulder pain. Pain reduction by PLA was not confirmed in four studies that compared PLA with no treatment. Three studies compared PLA with uterosacral block; intracervical block; and intrauterine topical anaesthesia. Two of these studies showed no significant difference in pain during the procedure. Compared to intrauterine instillation, PLA slightly reduced severe pain (from 8.3 to 7.6, on a 10-point pain scale), which may be negligible. This benefit appeared to be greater for women who required cervical dilatation. Two studies compared PLA with sedation. There were no statistically significant differences in pain during or after the procedure, postoperative analgesia requirement, adverse effects, patient satisfaction, and the operator's perception of analgesia.

Authors' conclusions

No technique provided reliable pain control in the 17 included studies. Some studies reported that women experienced severe pain (mean scores of 7 to 9 out of 10) during uterine intervention, irrespective of the analgesic technique used. We concluded that the available evidence fails to show whether paracervical block is inferior, equivalent or superior to alternative analgesic techniques, in terms of efficacy and safety, for women undergoing uterine interventions.

PLAIN LANGUAGE SUMMARY

Paracervical local anaesthesia for cervical dilatation and uterine interventions

Paracervical block involves injection of local anaesthetic around the cervix to numb nearby nerves. Cervical dilatation and uterine interventions (such as hysteroscopies, endometrial biopsies, fractional curettage, and suction terminations) can be performed without any analgesia or anaesthesia; with regional anaesthetic injections as with paracervical block; using oral or intravenous analgesics and sedatives; or under general anaesthesia. Many gynaecologists use paracervical block for uterine intervention but it is unclear how effective and safe this method is. We included 17 studies involving 1855 women undergoing uterine interventions who were randomly allocated to paracervical block or an alternative. We found that women had less pain during uterine intervention with paracervical block than with placebo injection (saline or water). However, in most studies this reduction was small. We did not find any evidence that paracervical block reduces residual pain after the procedure. Four studies that compared paracervical block with no treatment (not even a placebo injection) did not find any differences in level of pain experienced by women having hysteroscopies, evacuation of retained products of conception, and suction terminations. We found insufficient evidence to determine any differences in pain experienced by women having paracervical block compared to alternative regional anaesthetic methods, or the use of systemic analgesics and sedatives. Information on any important side effects was insufficient to determine if these are more common with paracervical block than with other methods of analgesia.

BACKGROUND

Indications for cervical dilatation and uterine intervention include abnormal uterine bleeding that does not respond to medical treatment, postmenopausal bleeding, and abortion. General anaesthesia (GA) provides adequate operating conditions for cervical dilatation and uterine intervention. However, there are some situations when GA is hazardous, for example when the patient is in a poor medical condition or when no anaesthesiologist is available. Paracervical local anaesthesia (PLA) offers an alternative to GA for cervical dilatation and uterine intervention in these women. Injection of local anaesthetic around the cervix, at the 'three and

nine o'clock' positions, anaesthetizes the second to fourth sacral nerve roots as they pass through Frankenhauser's plexus at a depth of 2 to 4 mm (Piyamongkol 1998). The advantages of PLA compared to GA are that it does not require general anaesthetic equipment nor the personnel trained to give GA. However, paracervical local anaesthetic should be administered by trained staff and resuscitation facilities should be available. Many gynaecologists use PLA for cervical dilatation and uterine intervention and its effectiveness is unclear. Premenopausal and postmenopausal as well as pregnant and non-pregnant women have different cervical conditions in terms of their anatomy and physiology. In this review we

compared the effectiveness and safety of PLA for cervical dilatation and uterine interventions versus no treatment, placebo, other methods of regional anaesthesia, sedation and systemic analgesia, and general anaesthesia.

OBJECTIVES

The objectives of this review were to determine the effectiveness and safety of PLA for cervical dilatation and uterine intervention versus no treatment, placebo, other methods of regional anaesthesia, sedation and systemic analgesia, and general anaesthesia.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled studies in which allocation was randomized or pseudo-randomized (alternate days, weeks, odd and even hospital numbers). We excluded concurrent cohort and observational studies.

Types of participants

We included women of any age who underwent cervical dilatation and uterine intervention for any indication.

Types of interventions

We Included studies in which at least one group had paracervical block. The comparison interventions were: placebo; no treatment; other regional anaesthesia; sedation and systemic analgesia. We did not compare one type of local anaesthetic with another.

Types of outcome measures

We included pain, adverse effects and patient satisfaction.

Primary outcomes

1. Pain during or after cervical dilatation and uterine intervention measured as categorical data, continuous data (for example on a visual analogue scale), or the requirement for additional analgesia;
2. adverse effects (such as nausea, vomiting, hypotension).

Secondary outcomes

1. Patient satisfaction (as defined by the study authors).

Search methods for identification of studies

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; [Appendix 1](#)), (*The Cochrane Library* 2006, Issue 1), MEDLINE on Silver Platter (1966 to January 2006; [Appendix 2](#)), EMBASE (January 1980 to January 2006; [Appendix 3](#)), and reference lists of articles.

We combined our search strategies with the Cochrane highly sensitive search strategy for randomized controlled studies phase one and two as contained in the Cochrane Handbook for Systematic Reviews of Interventions ([Higgins 2005](#)).

We searched for ongoing and recently published studies at www.controlled-studies.com.

We did not apply any language restrictions.

Data collection and analysis

Eligibility

We did not blind the names of the study authors, institutions, or journal of publication. Two authors (TT and US) independently evaluated the eligibility of studies from their title, abstract, and the full paper. We analysed the results of the randomized controlled studies that we had selected and graded their methodological quality for: concealment of allocation; blinding of the intervention administered; completeness of follow up; and blinding of outcome assessment. We used the Cochrane method for stratifying qualitative aspects of each study: 'A' for adequate; 'B' for unclear; 'C' for inadequate; and 'D' for not used ([Higgins 2005](#)). We resolved any disagreements through discussion. The third author (PL) evaluated disputed studies to obtain a consensus.

Data extraction

We used the standard methods of the Cochrane Anaesthesia Review Group. Two authors (TT and US) scrutinized all the titles and abstracts for their suitability and independently extracted data. One author (TT) checked the data and entered them into [Review Manager 5.0](#). We contacted the authors of any study that had missing data.

Statistical analyses

Where appropriate we analysed pooled data using [Review Manager 5.0](#) (RevMan). The method of meta-analysis was dependent on the nature of the outcomes. For categorical data (for example proportion of participants with an event) we related the number reporting an event to the number at risk in each group to derive a

relative risk (RR) and 95% confidence interval (CI). We pooled continuous differences between groups in the meta-analysis (for example pain relief on a visual analogue scale) as mean differences (MD) or standardized mean differences (SMD), as appropriate, with their 95% CI. As a general rule we used a fixed-effect model for calculation of summary estimates. When we suspected important heterogeneity, determined by visual inspection or the I^2 statistic for heterogeneity (Higgins 2003), we investigated differences in clinical and methodological factors between studies. We performed a sensitivity analysis for assessing the effect of quality of studies on the conclusions. We assessed the clinical significance of statistically significant differences between the groups. When meta-analysis was inappropriate we drew conclusions from the descriptive elements of the studies; methodological quality; number of studies with consistent findings; plausibility of the results; and the strength of the associations in the primary studies as well as consensus among authors.

We anticipated that we would conduct meta-analyses for the following comparisons.

1. Paracervical local anaesthesia versus placebo.
2. Paracervical local anaesthesia versus no anaesthesia.
3. Paracervical local anaesthesia versus other methods of regional anaesthesia.
4. Paracervical local anaesthesia versus systemic analgesia.
5. Paracervical local anaesthesia versus general anaesthesia.

RESULTS

Description of studies

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

We identified 1110 studies with our initial search strategies of which 97 had relevant titles and abstracts. We excluded 78 studies (see [Characteristics of excluded studies](#)). Titles and abstracts were unclear in three studies and we put them into studies awaiting assessment (Chaudhuri 1980; Regina 1987; Sen 1980). We identified 17 relevant studies with a total of 1855 women that were published in full. We included three studies of paracervical local anaesthesia versus sedation and systemic analgesia (Buppasiri 2005; Guida 2003; Mola 1996); eight studies versus placebo (Chanrachakul 2001; Chatfield 1970; Cicinelli 1998; Egziabher 2002; Glantz 2001; Lau 1999; Miller 1996; Titapant 2003); three studies versus other regional techniques (Finikiotis 1992; Kan 2004; Yazaci 2003); and four studies versus no anaesthesia (Carroll 2005; Gómez 2004; Kan 2004; Vercellini 1994). We did not find any studies of paracervical block versus general anaesthesia that met our inclusion criteria (see [Characteristics of included studies](#)).

Risk of bias in included studies

We graded allocation concealment as adequate in six studies (Carroll 2005; Cicinelli 1998; Glantz 2001; Gómez 2004; Lau 1999; Mola 1996); unclear in six studies (Buppasiri 2005; Chanrachakul 2001; Chatfield 1970; Miller 1996; Titapant 2003; Yazaci 2003); and inadequate in five studies (Egziabher 2002; Finikiotis 1992; Guida 2003; Kan 2004; Vercellini 1994). Seven of 17 studies reported adequately blinding women to their allocated intervention (Chanrachakul 2001; Chatfield 1970; Cicinelli 1998; Egziabher 2002; Glantz 2001; Lau 1999; Miller 1996). Four studies reported adequately blinding treatment providers to the allocated intervention (Chanrachakul 2001; Chatfield 1970; Glantz 2001; Lau 1999); and five studies reported adequately blinding the outcome assessors to the allocated intervention (Chanrachakul 2001; Chatfield 1970; Cicinelli 1998; Glantz 2001; Lau 1999). Three of these (Chatfield 1970; Cicinelli 1998; Glantz 2001) blinded assessors to outcomes other than abdominal pain. All studies completed follow up for all women.

Effects of interventions

We included 17 studies involving 1855 women. Studies compared paracervical block versus: placebo, no treatment, other types of regional anaesthesia, and systemic analgesia (and sedation). Outcomes included pain, adverse effects and patient satisfaction.

Paracervical local anaesthesia versus placebo

(Analysis 1.1 to Analysis 1.10)

Eight studies compared paracervical block with placebo (Chanrachakul 2001; Chatfield 1970; Cicinelli 1998; Egziabher 2002; Glantz 2001; Lau 1999; Miller 1996; Titapant 2003). Uterine interventions included hysteroscopy, endometrial biopsy, fractional curettage, and vacuum aspiration. The local anaesthetics used were lidocaine, chloroprocaine, and xylocaine (see [Characteristics of included studies](#) for details).

Pain during the procedure

Paracervical injection of local anaesthetic was 0.87 points (95% CI 0.14 to 1.60) less painful than injection of saline placebo on a 10-point pain scale (from about 4.5 with placebo to about 3.6 with PLA where a score of 0 means 'no pain' and a score of 10 means 'worst pain') (Analysis 1.1). In two studies (Lau 1999; Miller 1996) there was no evidence that paracervical block reduced pain during cervical dilatation (Analysis 1.2). Compared to placebo, paracervical block reduced pain during uterine interventions (endometrial biopsy, fractional curettage, suction evacuation, or aspiration) by the equivalent of two or three points on a 10-point pain scale (standardized mean difference (SMD) (Analysis 1.3). In two studies (Chatfield 1970; Egziabher 2002) paracervical block

reduced the risk of severe pain during uterine intervention (RR 0.16, 95% CI 0.06 to 0.74) but not the risk of any pain ([Analysis 1.4](#)). [Chanrachakul 2001](#) reported that paracervical block significantly reduced the median pain score during fractional curettage, from 6.0 to 4.0 (statement unsupported by a P value).

Postoperative pain

We did not find any evidence that paracervical block reliably reduced postoperative pain when compared to placebo injection ([Analysis 1.5](#); [Analysis 1.6](#); [Analysis 1.10](#)). In one study ([Egziabher 2002](#)) paracervical block did not reduce the summated risk of intraoperative and postoperative backache ([Analysis 1.9](#)). Paracervical block did not reduce the risk of shoulder pain at any time ([Analysis 1.9](#)).

Adverse effects

Paracervical block did not change the risk of sweating, nausea or vomiting ([Analysis 1.10](#)). In one study ([Lau 1999](#)) the risk of hypotension after paracervical block was greater than after placebo injection (RR 3.06, 95% CI 1.21 to 7.78). Three women out of 27 injected with lidocaine reported symptoms consistent with toxicity (tingling lips, dizziness) in [Miller 1996](#).

Paracervical local anaesthesia versus no anaesthesia

([Analysis 2.1](#) to [Analysis 2.2](#))

Four studies compared paracervical block versus no treatment ([Carroll 2005](#); [Gómez 2004](#); [Kan 2004](#); [Vercellini 1994](#)). In two studies women had hysteroscopies ([Carroll 2005](#); [Vercellini 1994](#)) and in two studies women had suction termination or evacuation of incomplete miscarriages ([Gómez 2004](#); [Kan 2004](#)).

Pain during the procedure and postoperative pain

[Kan 2004](#) found no evidence that paracervical block reduced median pain scores during or after suction termination under sedation when compared to no block. There was no evidence for significant differences in pain during hysteroscopy and endometrial biopsy in [Vercellini 1994](#) ([Analysis 2.1](#)). [Carroll 2005](#) reported no differences in pain scores measured immediately after hysteroscopy and 5 and 10 minutes later ([Analysis 2.2](#)). [Gómez 2004](#) reported no difference in intraoperative pain as recalled 10 minutes after the procedure.

Adverse effects

No study found evidence for differences in the risks of adverse effects.

Patient satisfaction

[Kan 2004](#) did not find evidence for differences in patient satisfaction.

Paracervical local anaesthesia versus other regional anaesthesia

([Analysis 3.4](#) to [Analysis 3.3](#))

Three studies ([Finikiotis 1992](#); [Kan 2004](#); [Yazaci 2003](#)) compared paracervical block to other local anaesthetic techniques: uterosacral block ([Finikiotis 1992](#)), intracervical block ([Kan 2004](#)), and intrauterine topical analgesia ([Yazaci 2003](#)).

Pain during the procedure

In one study ([Finikiotis 1992](#)) paracervical block did not reduce the risk of pain during hysteroscopy compared to uterosacral block (RR severe pain 0.17, 95% CI 0.42 to 3.27; RR moderate to severe pain 1.22, 95% CI 0.80 to 1.85). Paracervical block did not change median pain scores compared to intracervical block measured during or after suction termination under sedation ([Kan 2004](#)). [Yazaci 2003](#) reported that women in both groups experienced severe pain during endometrial biopsy; the paracervical block group (mean pain score 76.3 out of 100) experienced slightly less pain than the intrauterine local anaesthetic instillation group (mean pain score 83.2 out of 100) ([Analysis 3.1](#)).

Postoperative pain

Postoperative pain was slightly less in the paracervical group in [Yazaci 2003](#) ([Analysis 3.2](#)), mean difference (out of 100) 4.63 (95% CI 0.24 to 9.02).

Adverse effects

[Yazaci 2003](#) did not find any difference in the risk of a vasovagal reaction ([Analysis 3.3](#)).

Paracervical local anaesthesia versus systemic analgesia

([Analysis 4.1](#) to [Analysis 4.7](#))

Three studies compared paracervical block with systemic analgesics and sedatives: mefenamic acid ([Buppasiri 2005](#)); fentanyl and midazolam ([Guida 2003](#)); and pethidine and diazepam ([Mola 1996](#)). [Buppasiri 2005](#) studied women undergoing fractional curettage, [Guida 2003](#) studied women undergoing hysteroscopy, and [Mola 1996](#) studied women having bi-manual removal of retained placenta.

Pain during uterine intervention and postoperative pain

There was no evidence that paracervical block reduced median pain scores during or after uterine intervention when compared to mefenamic acid (Buppasiri 2005), or pethidine and diazepam (Mola 1996). There were no consistent differences in intraoperative and postoperative pain scores between paracervical block and treatment with midazolam and fentanyl in Guida 2003 (Analysis 4.1 to Analysis 4.3). Mola 1996 found no differences between paracervical block and combined analgesia and sedation in the risk of intraoperative pain identified by the women (Analysis 4.2) or the operator's perception of women's pain (Analysis 4.7).

Adverse effects

Guida 2003 reported no evidence for a difference in the risk of pallor, hypotension, or nausea and vomiting. Buppasiri 2005 reported no evidence for a difference in the risk of dizziness (Analysis 4.5).

Patient satisfaction

Guida 2003 reported no evidence for a difference in the risk of dissatisfaction (Analysis 4.6).

Paracervical local anaesthesia versus general anaesthesia

We did not find any eligible studies for this comparison. We found no studies that compared the effectiveness of paracervical block in premenopausal and postmenopausal women or in gynaecological and obstetric indications.

DISCUSSION

Summary of main results

Seventeen included studies compared paracervical block and other anaesthetic and analgesic methods for women undergoing uterine interventions in terms of effectiveness in pain control, adverse effects and patient satisfaction. Some studies had co-interventions (amnesic sedation or opioids), given to both intervention and control groups, however we found no differences in pain control in these studies. Premedications such as opioid are given to allay the patient's apprehension on entering an operating theatre and being placed in the lithotomy position. In these studies, where the premedication was given to both groups, analgesics were omitted to avoid confusion in pain assessment. We anticipated that a clinically significant difference in the need for pain relief or the risk of adverse events would be a 50% difference, but we did not find any

differences in effectiveness and safety between paracervical block and placebo or other anaesthetic and analgesic methods.

Overall completeness and applicability of evidence

We included 17 relevant studies involving 1855 women. Although we had planned to include five comparisons the available studies allowed only four. Eight included studies, with 754 women, compared paracervical block with placebo. Four studies (584 women), three studies (365 women), and three studies (283 women) compared paracervical block with no anaesthesia, other regional anaesthesia methods, and systemic analgesia, respectively. All 17 studies measured pain as an outcome. Six studies had information on adverse effects, two studies reported patient satisfaction, and two studies reported on postoperative analgesic requirements. The women included in this review were undergoing both obstetric (dilatation curettage, manual placenta removal, manual vacuum aspiration) and gynaecologic (hysteroscopy, fractional curettage, endometrial biopsy or ablation) interventions. The studies in this review included sufficient numbers of women, who received either paracervical block or other anaesthetic or analgesic methods, involved both obstetric and gynaecologic interventions and evaluated all major outcomes.

Quality of the evidence

Only 7 of the 17 included studies had adequate random allocation concealment but we could not perform sensitivity analyses to evaluate the robustness of the result. This was because we had more than one comparison and each comparison had a limited number of included studies. Only 7 of 17 included studies reported using some form of blinding. In conclusion, less than half of the included studies had adequate quality in terms of randomised allocation concealment and blinding.

Potential biases in the review process

We strictly followed the search strategies recommended by the Cochrane Anaesthesia Review Group (CARG). We searched all recommended databases and had access to all the potential studies identified except the three awaiting assessment (Chaudhuri 1980; Regina 1987; Sen 1980). We will add these awaiting studies in an update of the review. Since we used the recommended review process described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2005), any bias in the review should be minimal.

AUTHORS' CONCLUSIONS

Implications for practice

All of the techniques used in the 17 included studies failed to reliably prevent pain in conscious women having uterine interventions. The available evidence does not show if paracervical block is inferior, equivalent, or superior to the alternative analgesic techniques, either in terms of efficacy or safety.

Implications for research

Our systematic review showed that pain experienced by women having uterine interventions is inadequately controlled by paracervical block. The findings of the 17 included studies suggest that the other methods that were compared with paracervical block (local anaesthetic methods, sedation and systemic analgesics) also inadequately control the pain. Researchers should conduct systematic reviews of these other methods to confirm or refute this finding. The design of any future randomized controlled trials of techniques for controlling pain in women having uterine interventions without general anaesthesia should take into account the results of such systematic reviews.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Buppasiri 2005

Methods	Randomized controlled trial	
Participants	87 women, 40 years and over, undergoing outpatient fractional curettage for abnormal uterine bleeding (44 in PLA group and 43 in analgesia group). The authors excluded women with peptic ulcer, a known sensitivity to non-steroidal anti-inflammatory drugs, taking medications with known interactions with non-steroidal anti-inflammatories, who were sensitive to lignocaine, or unable to provide informed consent.	
Interventions	1. PLA: 2% lignocaine 5 ml injected into the lateral fornix at 3 and 9 o'clock at a depth of between 3 and 5 mm. Fractional curettage was performed 5 min after the paracervical injection. 2. Analgesic: mefenamic acid 500 mg orally two hours before the procedure.	
Outcomes	Pain was evaluated using a 10 cm visual analogue scale: Before the procedure 2. During endocervical curettage 3. Endometrial curettage 4. Immediately after curettage 5. 30 minutes after completing the procedure. Adverse effects: 1. Dizziness.	
Notes	Three women in each group could not tolerate the pain and needed intravenous pethidine.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	Randomly allocated

Carroll 2005

Methods	Randomized controlled trial	
Participants	58 women undergoing endometrial biopsy (27 in PLA and 31 in no anaesthesia group). Women were excluded for the following reasons: allergy to lidocaine, allergy to ibuprofen, refusal to participate, additional procedure (e.g. loop electrosurgical excision procedure, colposcopy etc), or inability to speak English.	
Interventions	1. PLA: 10 ml of 1% lidocaine injected paracervically at 2, 4, 8, and 10 o'clock positions and waited 3 to 5 minutes before biopsy (Pipelle biopsy). 2. No anaesthesia.	
Outcomes	Pain immediately before the procedure, immediately after the procedure, at 5 minutes, and at 10 minutes.	

Carroll 2005 (Continued)

Notes	We were unable to perform a subgroup analysis comparing cervical dilatation versus no cervical dilatation because results were not reported by intervention.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	Opaque sealed envelopes

Chanrachakul 2001

Methods	Randomized controlled trial	
Participants	140 women who underwent fractional curettage (70 in each of paracervical and saline groups). The exclusion criterion was an allergic reaction to lidocaine.	
Interventions	1. PLA: 1% lidocaine hydrochloride. 2. Placebo: 0.9% sodium chloride. Injection was with a 23-gauge spinal needle at 3 and 9 o'clock of the cervicovaginal reflection.	
Outcomes	Pain during and after the procedure.	
Notes	Using the visual analogue scale, each patient made four assessments of intensity of pain: 1. Pain immediately after insertion of the speculum and was for intensity of pain during insertion of the speculum 2. Immediately after curettage and was for intensity of pain during curettage 3. Intensity of pain immediately after curettage 4. 30 minutes after curettage for intensity of pain at that time. The repeated injection was limited to 10 ml of 1% lidocaine. No patient asked for lidocaine during the procedure or asked to leave the study.	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Chatfield 1970

Methods	Randomized controlled trial	
Participants	100 consecutive women with an incomplete abortion; uterine size varied from 8 to 16 weeks and in the majority the cervix was open and required no further dilatation for the evacuation procedure (50 in each: PLA and placebo group).	

Chatfield 1970 (Continued)

Interventions	1. PLA: 0.25% bupivacaine with 1:400,000 adrenaline, 5 ml. 2. Normal saline, 5 ml. Injected through the vaginal wall of each lateral fornix, approximately 1 cm from the cervix and at eight and four o'clock, half-an-hour prior to evacuation.	
Outcomes	Patient's impression of discomfort during evacuation.	
Notes	“Promazine 25 mg and promethazine 25 mg given after the block to allay the patient's natural apprehension on entering an operating theatre and being placed in the lithotomy position awake. Analgesics were omitted from the premedication to avoid confusion in the assessment of the efficacy of the anaesthetic. The discomfort was recorded as being none, slight, moderate or severe.”	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	Random selection

Cicinelli 1998

Methods	Randomized controlled trial	
Participants	72 postmenopausal women undergoing diagnostic hysteroscopy and endometrial biopsy for uterine bleeding. All women had been amenorrhoeic and free of oestrogen replacement for at least one year.	
Interventions	1. PLA: 10 ml of 1.5% mepivacaine. 2. Placebo: 10 ml of saline. Injected at the junction of the cervix and vagina at the 4 and 8 o'clock position.	
Outcomes	Pain Vasovagal reactions.	
Notes	Visual analogue scale contained a 20-cm scale for the patient to record responses as follows: 0 cm, no pain; 5 cm, low pain; 10 cm, moderate pain; 15 cm, severe pain; and 20 cm, excruciating pain.	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Yes	"Sealed envelopes containing computer-generated block randomization numbers"

Egziabher 2002

Methods	Randomized controlled trial	
Participants	142 women with incomplete abortion underwent manual vacuum aspiration. Inclusion criteria: less than 16 weeks of gestation. Exclusion criteria: evidence of infections, blood pressure more than 140/90 mm Hg, diabetes, cardiac diseases, severe anaemia, cervix less than 1.5-2 cm dilated, allergy to lidocaine, respiratory distress and acute pelvic inflammatory disease.	
Interventions	1. PLA: 1% lidocaine. 2. Placebo: sterile water. Injected about 2 ml of lidocaine or placebo just under the epithelium not deeper than 2-3 mm at 3 and 9 o'clock.	
Outcomes	Pain Side effects: abdominal pain, shoulder tip pain, and backache.	
Notes	We analysed data during and after the procedure only, not data before the procedure.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	No	“Selected women using random tables”

Finikiotis 1992

Methods	Controlled clinical trial	
Participants	120 women who were referred from general practitioners and other gynaecologists for the investigation of a variety of gynaecological complaints and underwent outpatient hysteroscopy.	
Interventions	1. PLA: 16-20 ml of 1% lidocaine using a paracervical block after a small amount (<0.5 ml) was injected into the anterior lip of the cervix for placement of a tenaculum. 2. USB: 2ml of 2% lidocaine with 1:80,000 adrenaline into each uterosacral ligament. A small amount (<0.5 ml) was injected into the anterior lip of the cervix which was then grasped with a tenaculum.	
Outcomes	Pain.	
Notes	We used the cut-off point at 0-3.3 = no pain and 3.4 to 10 = pain.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	No	Randomized by odd or even unit numbers

Glantz 2001

Methods	Randomized controlled trial
Participants	79 pregnant women at least 18 years old, between 7 and 12 weeks' gestation, undergoing elective termination of pregnancy by mechanical aspiration. Women were excluded if they had significant medical complications that put them at risk for complications in the clinic setting, or if they had a history or sensitivity to local anaesthetic.
Interventions	1. PLA: 10 ml of 1% chlorprocaine. 2. Placebo: 10 ml of saline. Group A: 3-5-7-9 o'clock (5-2-2-5 ml, 1% chlorprocaine) Group B: 4-8 o'clock (7-7 ml, 1% chlorprocaine) Group C: 3-5-7-9 o'clock (5-2-2-5 ml, normal saline) Group D: 4-8 o'clock (7-7 ml, normal saline). The day before the procedure, a nurse practitioner inserted one laminaria into the cervical canal, women took 600 mg of ibuprofen 1 hour before aspiration. The laminaria were removed on the day of the termination procedure.
Outcomes	Pain immediately following paracervical block administration, after aspiration, and arrival in the recovery room.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	"Ordered opaque sealed envelopes"

Guida 2003

Methods	Randomized controlled trial
Participants	166 women with surgically treatable lesions associated with infertility or abnormal uterine bleeding (82 in the PLA group and 84 in the SA group). Exclusion criteria were menopausal women (FSH > 40 mIU/ml, 17 beta-estradiol < 20 pg/ml), and/or pregnancy (positive beta-hCG test), and a history of anaesthetic or surgical complications.
Interventions	1. PLA: 10 ml of 1% mepivacaine hydrochloride injected with 22-gauge spinal needle at four sites (3, 5, 7 and 9 o'clock positions) at the junction of the cervix and vagina. 2. SA: 0.5 mg of atropine, 0.25 mg of fentanyl, followed by an intravenous slow injection of 2.0 mg of midazolam.
Outcomes	Pain. Adverse effect: 1. Pallor or hypotension 2. Nausea and vomiting. Patient satisfaction.
Notes	

Guida 2003 (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	No	"Women randomized into two groups using a computer-generated list in blocks of two"

Gómez 2004

Methods	Randomized controlled trial	
Participants	215 women who were at 12 weeks of gestation or less with incomplete abortion (107 in no anaesthesia group and 108 in paracervical group). Women with active infections, severe illness, psychiatric disorders, or allergies to lidocaine were excluded.	
Interventions	1. PLA: Psychological support and paracervical block using 1.0% lidocaine 5 ml injected slowly to a depth of 0.5 cm in the cervix-vaginal joint at 4 or 5 or 7 or 8 o'clock positions. 2. Placebo: Psychological support but no paracervical block.	
Outcomes	Intraoperative pain. Changes in the level of pain: before and during the procedure. The need to suspend the procedure or administer anaesthetics medicaments or parenteral sedatives; the need for other parenteral analgesics. Existence of intraoperative and postoperative complications.	
Notes	We analysed pain and administered anaesthetic medicaments or parenteral sedatives.	

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	"Sealed sequential opaque envelopes"

Kan 2004

Methods	Randomized controlled trial	
Participants	134 women attending for suction termination of pregnancy under local anaesthesia: age over 16 years, normal general and gynaecological examination, up to 12-weeks gestation on the day of recruitment and size of the uterus on pelvic examination compatible with estimated duration of pregnancy. Exclusions: Allergy to lidocaine, history of severe respiratory or cardiac disease, severe and recurrent liver disease, myasthenia gravis, psychiatric conditions requiring medication, contraindications to prostaglandins use.	
Interventions	1. PLA: 10 ml of 1% lidocaine injected at the vaginal vault. 2. Intracervical: 10 ml of 1% lidocaine injected at the cervix 2.5 cm beneath the mucosa. 3. No local injection. All women received conscious sedation 2 mg midazolam and 25 mcg fentanyl.	

Kan 2004 (Continued)

Outcomes	Pain before the operation, just after the operation, and 1 hour after suction evacuation Need for additional analgesia. Adverse effects. Patients' satisfaction.	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	No	A nurse used an open randomized allocation list

Lau 1999

Methods	Randomized controlled trial	
Participants	99 women undergoing outpatient hysteroscopy and endometrial biopsy for abnormal uterine bleeding.	
Interventions	1. PLA: 10 ml of 2% lidocaine. 2. Placebo: 10 ml of normal saline. Paracervical block was performed using a 22-gauge spinal needle and the solution was given at 3, 5, 7, and 9 o'clock of the paracervical region in divided doses.	
Outcomes	Pain felt at different stages of the procedure. Vasovagal reaction.	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	Number put inside sealed envelope.

Miller 1996

Methods	Randomized controlled trial	
Participants	52 women presenting for pregnancy termination (27 in PLA group and 25 in placebo group). Exclusion criteria: did not speak English, allergy to lidocaine, had used cocaine within 24 hours, or were greater than 14 weeks' gestation as estimated by ultrasound measurements.	
Interventions	1. PLA: 20 ml of 1% lidocaine. 2. Placebo: 20 ml of 0.9% sodium chloride. * I.V. 50 microgram fentanyl given before procedure if requested.	

Miller 1996 (Continued)

Outcomes	Pain: after speculum placement, after cervical canal dilation and/or insertion of the cannula, after aspiration, and then 30 minutes after the procedure. Vasovagal reactions.	
Notes	Block was repeated on request by one woman who found dilatation painful.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	“All study syringes were made up at the beginning of each clinic session and labelled with random five-digit numbers. Syringes were then mixed in a draw and withdraw one at a time”

Mola 1996

from 1990

Methods	Randomized controlled trial	
Participants	30 women undergoing bi-manual removal of retained placentas.	
Interventions	1. PLA: women 40-59 kg received 20 ml, 60-79 kg received 32 ml and weighing > 79 kg received 40 ml of 0.5% lidocaine, respectively [these women received premedication - see notes]. 2. Diazepam and pethidine group: women 40-59 kg received pethidine 50 mg and diazepam 5 mg, women 60-79 kg received pethidine 75 mg and diazepam 7.5 mg, and weighing > 79 kg received pethidine 100 mg and diazepam 10 mg, respectively.	
Outcomes	Patients' perception of pain experienced during the procedure. The operator's perception of the patients' pain and the difficulty of the placental removal. Immediate and late complications.	
Notes	Both groups were premedicated with intravenous pethidine 0.5 mg/kg and diazepam 1 mg/10 kg between 30 and 60 minutes before the procedure.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	"Sealed envelopes"

Titapant 2003

Methods	Randomized controlled trial	
Participants	70 women with unknown cause of abnormal vaginal bleeding who underwent fractional curettage (35 in PLA group and 35 in placebo group). All women were healthy, except for their bleeding, did not have diabetes mellitus or hypertension. Women who had abnormal coagulation or a history of chronic pelvic pain were excluded.	

Titapant 2003 (Continued)

Interventions	1. PLA: 1% xylocaine without adrenaline. 2. Placebo group: normal saline. Infiltrated around cervix just before the procedure was performed.	
Outcomes	Pain during the procedure and 30 minutes afterwards.	
Notes	No explanation of what pain scale was - what was the smallest and largest possible numerical values and what did they mean? We analysed pain during endometrial curettage only, not during endocervical curettage.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	“Randomly allocated to two groups”

Vercellini 1994

Methods	Randomized controlled trial	
Participants	177 women with excessive uterine bleeding for at least 3 months. Excluded: pregnancy, menopausal (FSH >29 mIU/mL), genital infections, previous cervical surgery or hysteroscopies, severe cardiac disease, sensitivity to local anaesthetic.	
Interventions	1. PLA: 10 ml of 1% mepivacaine hydrochloride solution injected with a 22-gauge spinal needle at four sites at 3, 5, 7, and 9 o'clock positions at the junction of the cervix and vagina. 2. No anaesthesia.	
Outcomes	Lower abdominal and pelvic pain at hysterectomy and endometrial biopsy.	
Notes		
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	No	"A randomization list was used to allocate subjects"

Yazaci 2003

Methods	Randomized controlled trial	
Participants	114 woman undergoing endometrial biopsy for abnormal uterine bleeding . All women were multiparous without history of allergy to lidocaine or any other medication. Women suspected to be pregnant were excluded.	

Yazaci 2003 (Continued)

Interventions	Women were randomly assigned into four groups: Group A (Placebo group): intrauterine instillation of 2 ml of 0.9% saline solution Group B: intrauterine instillation of 2ml of 20 mg/ml lidocaine hydrochloride Group C: paracervical injection of 1% lidocaine (volume unclear) Group D: intrauterine instillation of 2ml of 20 mg/ml lidocaine hydrochloride and paracervical injection of 1% lidocaine (volume unclear).	
Outcomes	Pain: during the application of the anaesthetic; during cervical dilation; during endometrial biopsy; 15 minutes after the procedure. Adverse effects.	
Notes	We compared PLA alone (group B) with intrauterine instillation of lidocaine (group C). We also analysed data comparing with and without cervical dilatation among groups.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	“Women were randomly assigned”

PLA = Paracervical local anaesthesia

GA = General anaesthesia

SA = Systemic analgesia

D & C = Dilatation and curettage

GA = General anaesthesia

CVS = Cardiovascular system

RS = Respiratory system

ml = millilitre

mg = milligram

mcg = microgram

i.v. = intravenous

kg = kilogram

sec = second

USB = Uterosacral block

Characteristics of excluded studies [ordered by study ID]

Agostini 2003	The intervention of this study was performed using neither anaesthesia nor analgesia.
Amyot-Legault 1981	This study was not a randomized controlled study.
Bain 2001	The intervention for this study was intracervical not paracervical block.

(Continued)

Baskett 1974	This study was excluded because a comparison between different strengths of bupivacaine. No direct comparison between procedures.
Bradley 1995	The intervention of this study was performed under neither anaesthesia nor analgesia
Broadbent 1992	The intervention for this study was intracervical not paracervical block
Canni 2001	All women received paracervical block. No comparison between paracervical block and other anaesthesia but evaluated the role of periorificial infiltration of local anaesthetic.
Cetin 1997	All women received paracervical block and assessed the effect of deep or regular injection of local anaesthetics.
Chen 1994	This study was excluded because the intervention was not cervical dilatation and a uterine intervention
Coker 1968	This study is case series, no comparison group.
Duggan 1999	All women tested all-in-one paracervical block and intravenous sedation. No direct comparison between procedures.
Duncan 2005	The intervention of this study was not cervical dilatation and uterine intervention but colposcopically directed biopsy and anaesthetic or placebo was injected into the biopsy site and treatment with coagulator, not paracervical block.
Edelman 2004	All women received paracervical block and compared between intrauterine lidocaine and saline infusion to study the effects on perceived patient pain.
Esteve 2002	The intervention for this study is intracervical not paracervical block.
Fernandez 1997	This study was not a randomized controlled study.
Ferry 1994	This study was not a randomized controlled study.
Formiga-Filho 1974	This study was a case series, no comparison group.
Gad 1967	This study was not a randomized controlled study.
Grimes 1979	This study was excluded because no clinically relevant outcomes (pain or nausea and vomiting) were reported. There were only operative complications (uterine haemorrhage, uterine perforation, intra-abdominal haemorrhage, cervical injury, fever, blood transfusion, cervical suture, laparotomy, hysterotomy or hysterectomy) shown.
Guasch 2005	This study was excluded because no clinically relevant outcomes were reported and the objective of the study was to compare the prolactin and stress hormone response to surgical stimulus under various anaesthetic techniques.
Gudgeon 1968	This study was excluded because comparison between different strengths of bupivacaine. No direct comparison between procedures.

(Continued)

Harper 1994	This study was excluded because the intervention was not cervical dilatation and uterine intervention with comparison between paracervical and intracervical block.
Harper 1998	This study was excluded because the intervention was not cervical dilatation and uterine intervention.
Hasham 1993	This study was excluded because performed paracervical block following ablation of the endometrium.
Hedberg 1966	This study was a case series, no comparison group.
Jensen 1984	This study was excluded because the intervention was in the first stage of labour without uterine intervention.
Johnson 1989	This study was excluded because the intervention was not cervical dilatation and uterine intervention.
Johnson 1996	This study was excluded because the intervention was not cervical dilatation and uterine intervention.
Kamat 1979	This study compared paracervical and pericervical block. No direct comparison between paracervical block and other anaesthesia.
Kaya 2004	All women tested all-in-one paracervical block and intravenous sedation. No direct comparison between procedures.
Kun 1999	The intervention for this study was intracervical not paracervical block.
Lee 1986	This study was excluded because the intervention was not cervical dilatation and uterine intervention.
Lee 1998	This study was excluded because the intervention was not cervical dilatation and uterine intervention.
Lewis 1971	This study was not a randomized controlled clinical study.
Littlepage 1969	This study was not a randomized controlled clinical study.
Longhi 1996	This study was excluded because a non-randomized controlled study and all women received paracervical and pudendal block.
Mackay 1985	This study was excluded because no clinically relevant outcomes (pain, nausea and vomiting) were reported. There were only operative complication (uterine haemorrhage, uterine perforation, intra-abdominal haemorrhage, cervical injury, fever, blood transfusion, cervical suture, laparotomy, hysterotomy or reported (fever, blood transfusion, unintended abdominal surgery, retained products of conception, postoperative haemorrhage, repeat curettage).
Makris 2001	The procedure in this study was performed without any kind of anaesthesia.
Mckenzie 1978	All women received paracervical block using modified jet injector compare with standard syringe and needle technique. No comparison between paracervical block and other anaesthesia.
Mercorio 2002	The intervention for this study was intracervical not paracervical block.

(Continued)

Moller 1978	This study was excluded because no clinically relevant outcomes (pain, nausea and vomiting) were reported.
Nielsen 1975	All women tested all-in-one paracervical block and intravenous sedation. No direct comparison between procedures.
Nielsen 1988	This study had many different co-interventions in each group, not comparing PLA alone with other anaesthesia.
O'Neal 2003	This study was excluded because the intervention was not cervical dilatation and uterine intervention.
Owalabi 2005	The intervention for this study not paracervical block alone but combined intracervical block.
Oyama 2003	The intervention of this study was not cervical dilatation and uterine intervention but colposcopically directed biopsy and lidocaine was injected into the biopsy site, not paracervical block.
Peretz 1982	This study was not a randomized controlled study.
Peters 1978	This study was excluded because a comparison between intracervical and paracervical block.
Phair 2002	All women received paracervical block and assessed the effect on pain of waiting between injection and procedure.
Picton 1968	This study was excluded because a comparison between different strengths of bupivacaine. No direct comparison between procedures.
Prest 1976	This study was not a randomized controlled study.
Raeder 1992	This study had many different co-interventions in each group, not comparing PLA alone with other anaesthesia.
Ragab 1978	This study was excluded because no clinically relevant outcomes.
Rattanachaiyanont	All women received paracervical block and compared between intrauterine lidocaine and saline infusion to study the effectiveness of intrauterine anaesthesia for pain relief.
Readman 2004	This study was a review, not a randomized controlled study.
Reguer Noriega 1973	This study was a case series, no comparison group.
Rogstad 1992	This study was excluded because the intervention was not cervical dilatation and uterine intervention.
Rotchell 1976	This study was a case series, no comparison group.
Ruoss 1968	This study was excluded because a comparison between different strengths of bupivacaine. No direct comparison between procedures.
Sammarco 1993	This study was excluded because the intervention was not cervical dilatation and uterine intervention

(Continued)

Sandmire 1974	This study was not a randomized controlled study.
Santonja 1974	This study was a case series, no comparison group.
Scott 1968	This study was excluded because a comparison between different strengths of bupivacaine. No direct comparison between procedures.
Shapiro 1975	All women tested all-in-one paracervical block and other sedation or stereophonic headphones. No direct comparison between procedures.
Stefanidis 1998	This study was excluded because the intervention was not cervical dilatation and uterine intervention.
Strausz 1971	This study was not a randomized controlled study.
Stuart 1993	This study was excluded because the intervention was not cervical dilatation and uterine intervention.
Teramo 1975	This study was excluded because a comparison between different strengths of etidocaine. No direct comparison between procedures.
Thonneau 1998	This study was not a randomized controlled study and no clinically relevant outcomes.
Toth 2000	This study was not a randomized controlled study.
Van Praagh 1967	This study was not a randomized controlled study.
Walden 1973	This study was not a randomized controlled study.
Wallage 2003	The intervention for the study not paracervical block alone but combined with intracervical block.
Whitehouse 1968	This study was excluded because a comparison between different strengths of bupivacaine. No direct comparison between procedures.
Wiebe 2005	All women tested all-in-one paracervical block and intravenous sedation. No direct comparison between procedures.
Willdeck 1975	This study was excluded because no direct comparison between the procedure but compared different strengths of etidocaine.
Winkler 1997	This study was excluded because no clinically relevant outcomes.
Wong 2002	All women received paracervical block and conscious sedation. No comparison between paracervical block but evaluated the role of conscious sedation.

Characteristics of studies awaiting assessment *[ordered by study ID]***Chaudhuri 1980**

Methods	not yet assessed
Participants	not yet assessed
Interventions	not yet assessed
Outcomes	not yet assessed
Notes	

Regina 1987

Methods	not yet assessed
Participants	not yet assessed
Interventions	not yet assessed
Outcomes	not yet assessed
Notes	

Sen 1980

Methods	not yet assessed
Participants	not yet assessed
Interventions	not yet assessed
Outcomes	not yet assessed
Notes	

DATA AND ANALYSES

Comparison 1. Paracervical versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on paracervical injection	2	178	Mean Difference (IV, Random, 95% CI)	-0.87 [-1.60, -0.14]
2 Pain dilating cervix	2	151	Std. Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.57, 0.07]
3 Pain during uterine intervention	5		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 Pain when the uterus is distended by carbon dioxide	1		Std. Mean Difference (IV, Random, 95% CI)	Not estimable
3.2 hysteroscopy	1		Std. Mean Difference (IV, Random, 95% CI)	Not estimable
3.3 Endometrial biopsy	2		Std. Mean Difference (IV, Random, 95% CI)	Not estimable
3.4 Uterine curettage	1		Std. Mean Difference (IV, Random, 95% CI)	Not estimable
3.5 Suction evacuation or aspiration	2		Std. Mean Difference (IV, Random, 95% CI)	Not estimable
4 Pain during uterine intervention	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Risk of any pain	2	242	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.54, 1.34]
4.2 Risk of severe pain	2	242	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.04, 0.74]
5 Postoperative pain	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Immediately after the procedure	3	223	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-0.92, 0.24]
5.2 15 minutes after the procedure	1	72	Std. Mean Difference (IV, Random, 95% CI)	-0.94 [-1.43, -0.45]
5.3 30 minutes after the procedure	3	221	Std. Mean Difference (IV, Random, 95% CI)	0.03 [-0.29, 0.35]
6 Postoperative abdominal pain	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 Immediately after surgery	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.2 30 minutes after surgery	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
7 Postoperative abdominal pain	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.1 Immediately after surgery	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
7.2 30 minutes after surgery	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
8 Back pain	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.1 During procedure	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
8.2 15 minutes after procedure	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
8.3 30 minutes after procedure	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
9 Shoulder pain	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 During the procedure	2	144	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 5.39]
9.2 After the procedure	2	241	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.51, 3.49]
10 Adverse effects	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Nausea/vomiting	3	429	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.02, 2.80]
10.2 Sweating	1	142	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.70, 1.67]
10.3 Hypotension	2	171	Risk Ratio (M-H, Random, 95% CI)	3.06 [1.21, 7.78]

Comparison 2. Paracervical versus no anaesthesia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain during uterine intervention	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 Hysteroscopy	1		Mean Difference (IV, Random, 95% CI)	Not estimable
1.2 Endometrial biopsy	1		Mean Difference (IV, Random, 95% CI)	Not estimable
2 Postoperative pain at different times	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Immediately after the procedure	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.2 5 minutes after the procedure	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.3 10 minutes after the procedure	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable

Comparison 3. Paracervical block versus other regional anaesthesia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain during anaesthetic application	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Pain during uterine intervention: continuous	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Endometrial biopsy	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3 Postoperative pain at different time: continuous	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 15 minutes after the procedure	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
4 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 vasovagal reactions	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable

Comparison 4. Paracervical versus systemic analgesia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain during uterine intervention	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 hysteroscopic electrosurgery	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
2 Pain during uterine intervention	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Postoperative pain	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 at 15 minutes	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.2 at 1 hour	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable

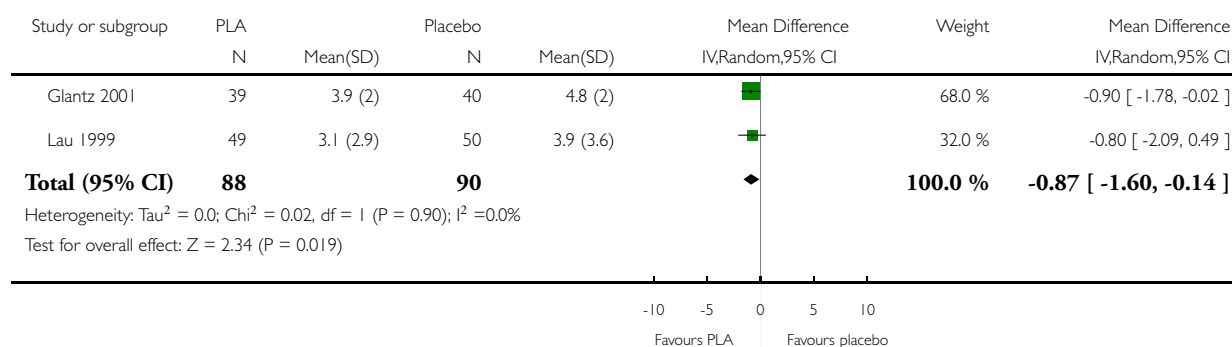
3.3 at 24 hours	1	Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.4 at 3 days	1	Mean Difference (IV, Fixed, 95% CI)	Not estimable
4 Requirement for postoperative analgesics	1	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Adverse effects	2	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 Pallor or hypotension	1	Risk Ratio (M-H, Random, 95% CI)	Not estimable
5.2 Nausea and vomiting	1	Risk Ratio (M-H, Random, 95% CI)	Not estimable
5.3 Dizziness	1	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6 Patient satisfaction	1	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Operator's perception of the analgesia	1	Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Paracervical versus placebo, Outcome 1 Pain on paracervical injection.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 1 Paracervical versus placebo

Outcome: 1 Pain on paracervical injection

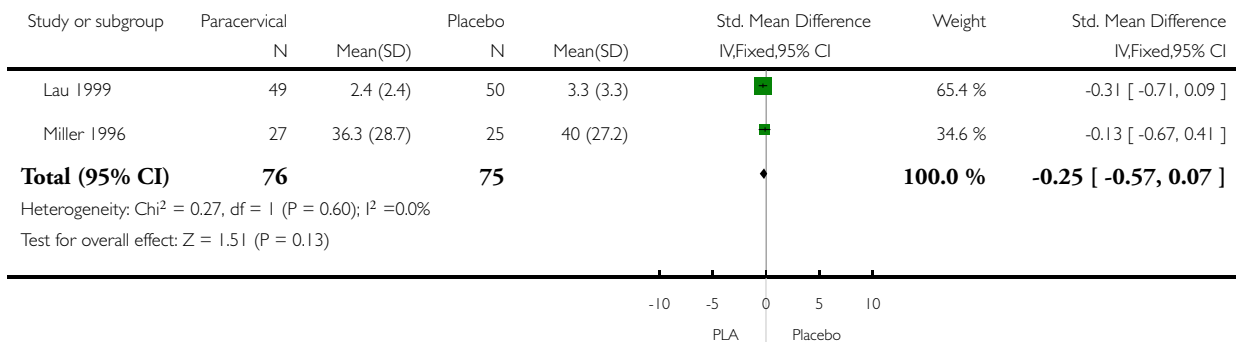


Analysis 1.2. Comparison 1 Paracervical versus placebo, Outcome 2 Pain dilating cervix.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 1 Paracervical versus placebo

Outcome: 2 Pain dilating cervix

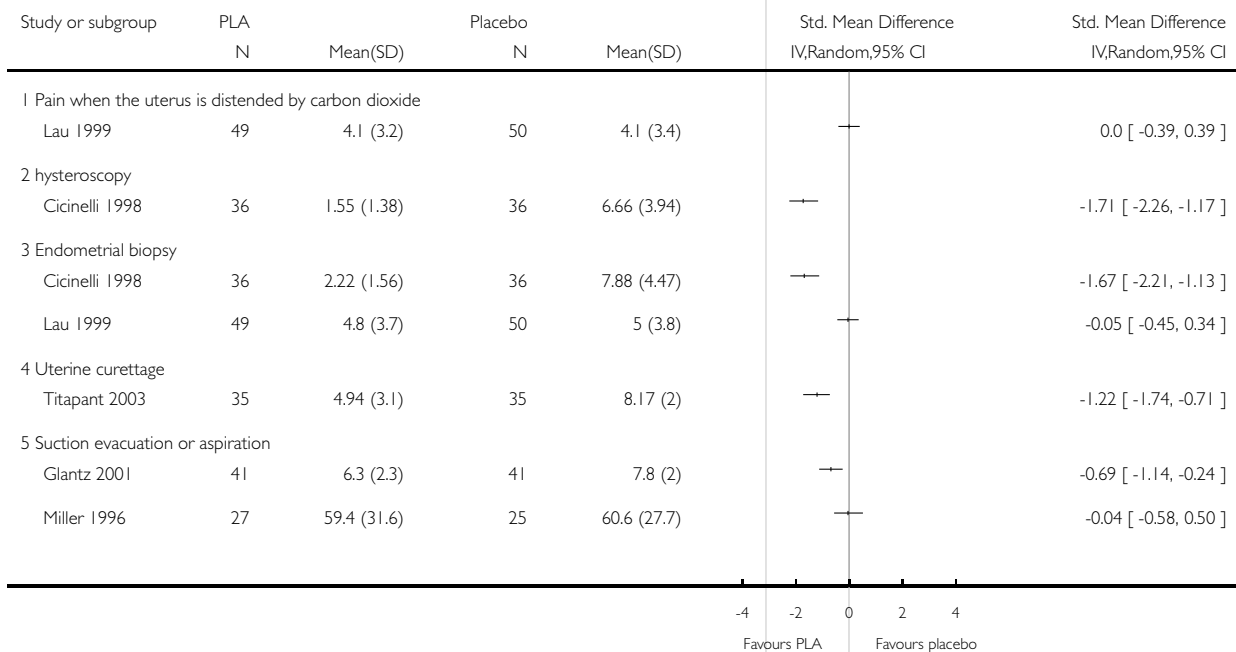


Analysis 1.3. Comparison 1 Paracervical versus placebo, Outcome 3 Pain during uterine intervention.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 1 Paracervical versus placebo

Outcome: 3 Pain during uterine intervention

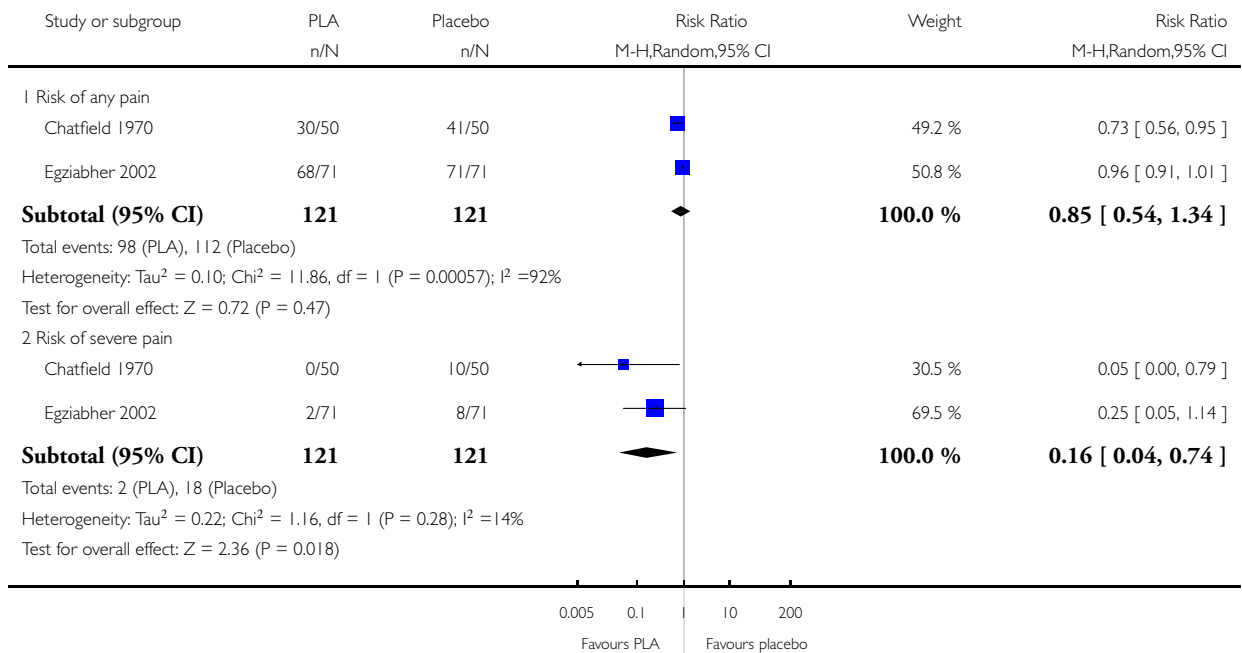


Analysis 1.4. Comparison 1 Paracervical versus placebo, Outcome 4 Pain during uterine intervention.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 1 Paracervical versus placebo

Outcome: 4 Pain during uterine intervention

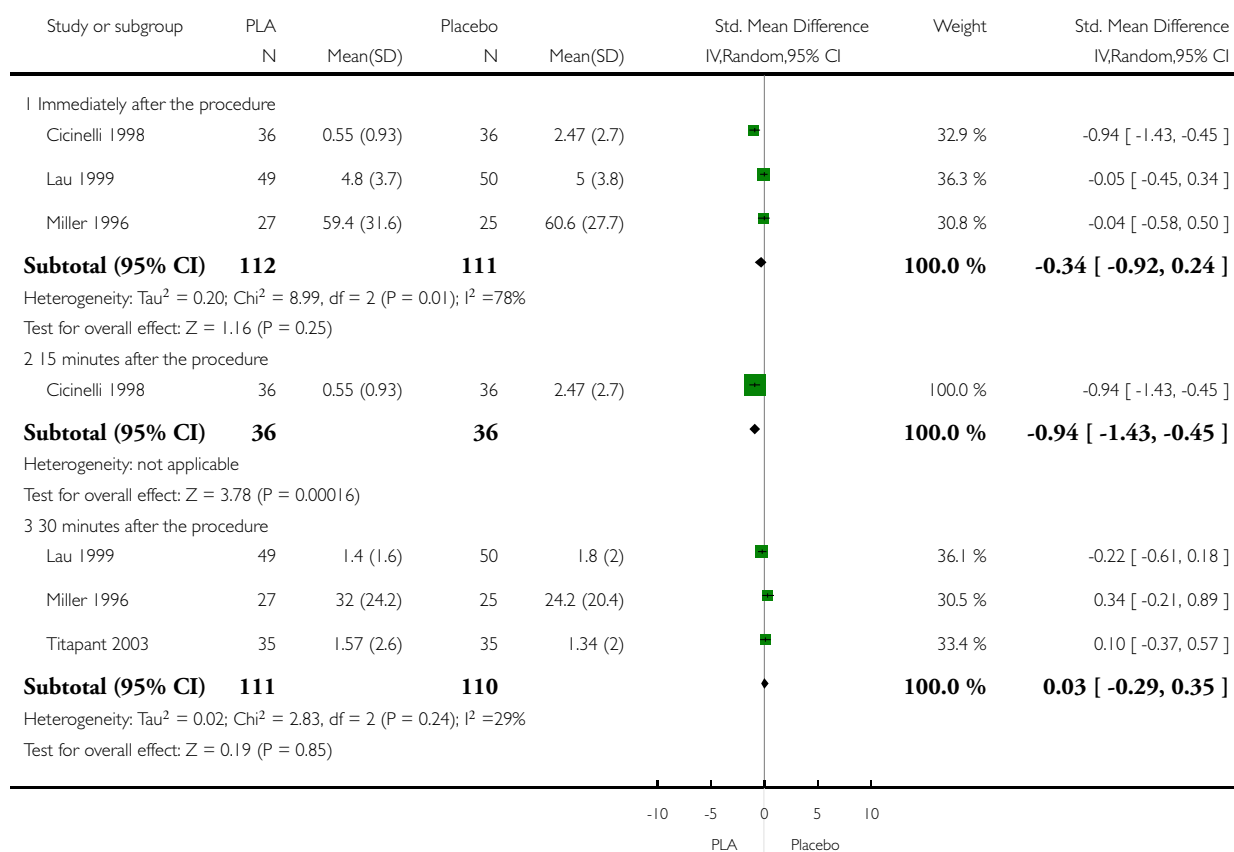


Analysis 1.5. Comparison 1 Paracervical versus placebo, Outcome 5 Postoperative pain.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 1 Paracervical versus placebo

Outcome: 5 Postoperative pain

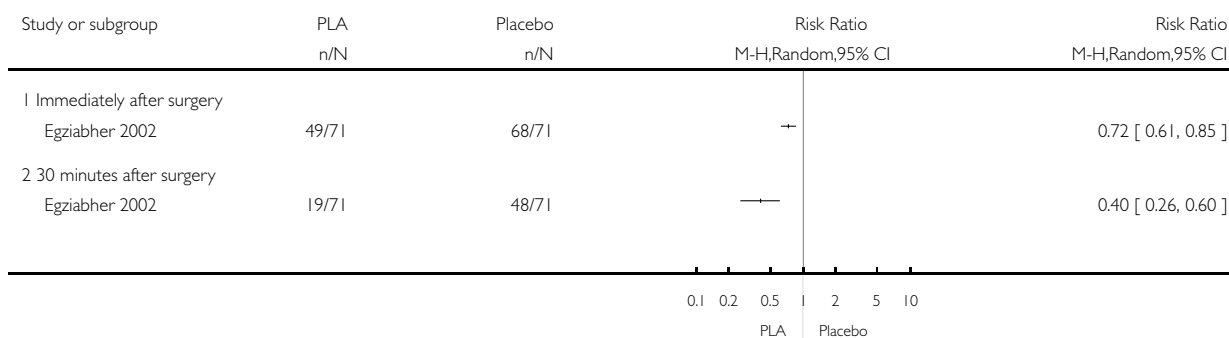


Analysis 1.6. Comparison 1 Paracervical versus placebo, Outcome 6 Postoperative abdominal pain.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 1 Paracervical versus placebo

Outcome: 6 Postoperative abdominal pain

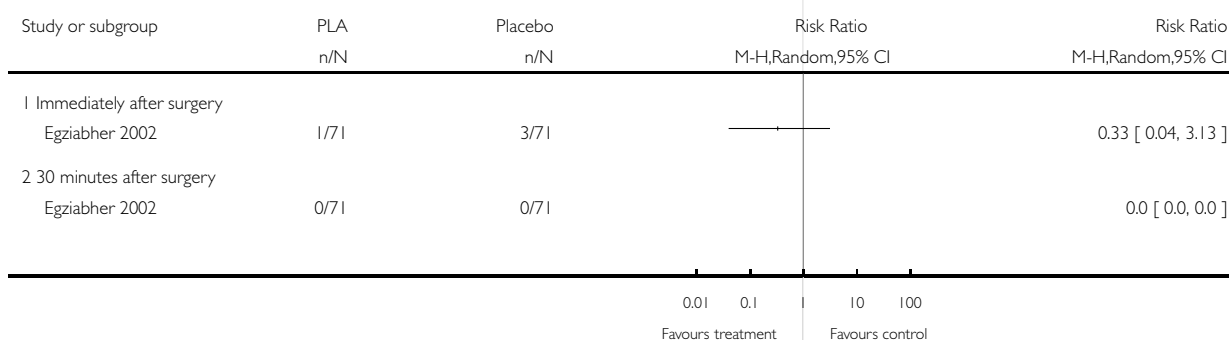


Analysis 1.7. Comparison 1 Paracervical versus placebo, Outcome 7 Postoperative abdominal pain.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 1 Paracervical versus placebo

Outcome: 7 Postoperative abdominal pain

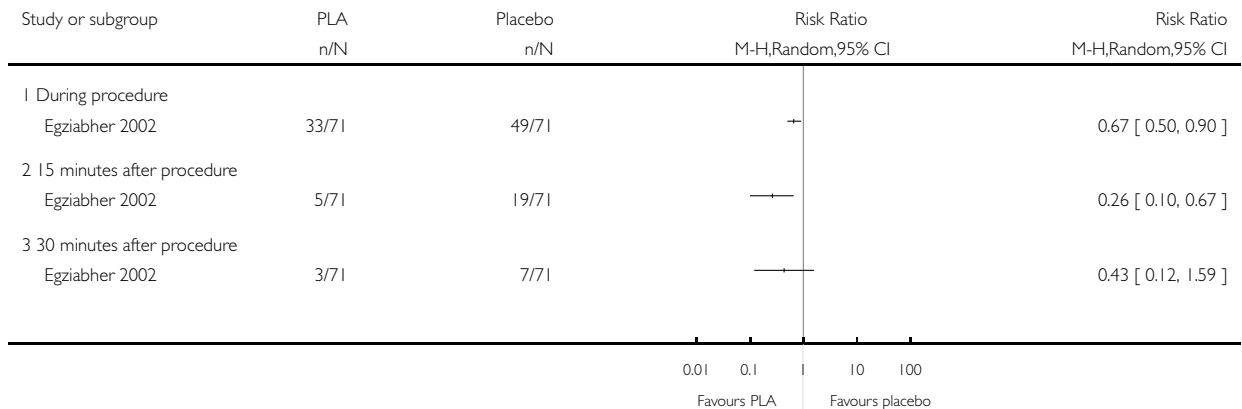


Analysis 1.8. Comparison 1 Paracervical versus placebo, Outcome 8 Back pain.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 1 Paracervical versus placebo

Outcome: 8 Back pain

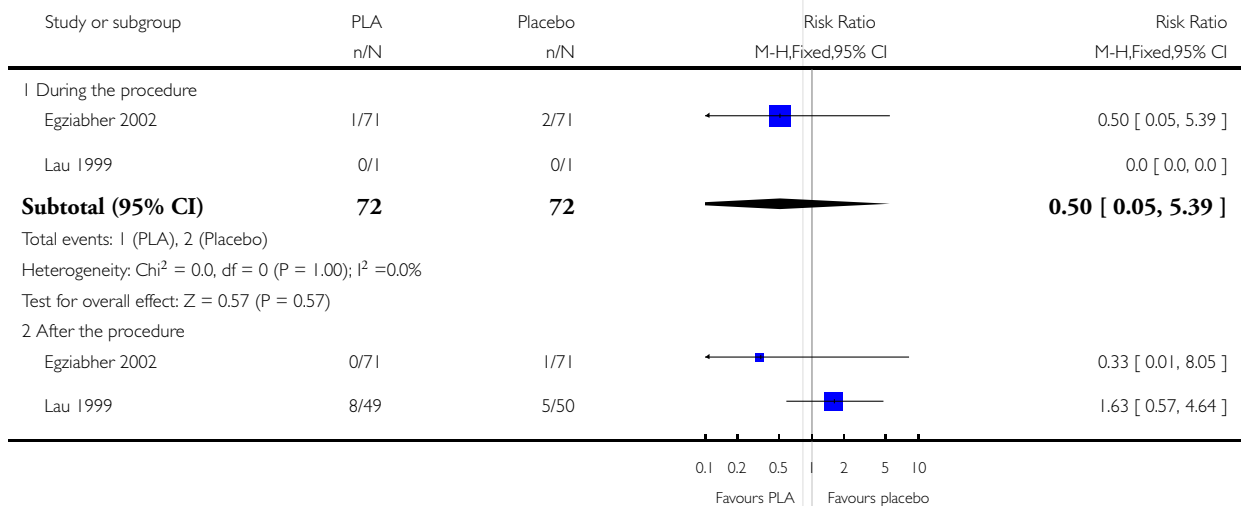


Analysis 1.9. Comparison 1 Paracervical versus placebo, Outcome 9 Shoulder pain.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

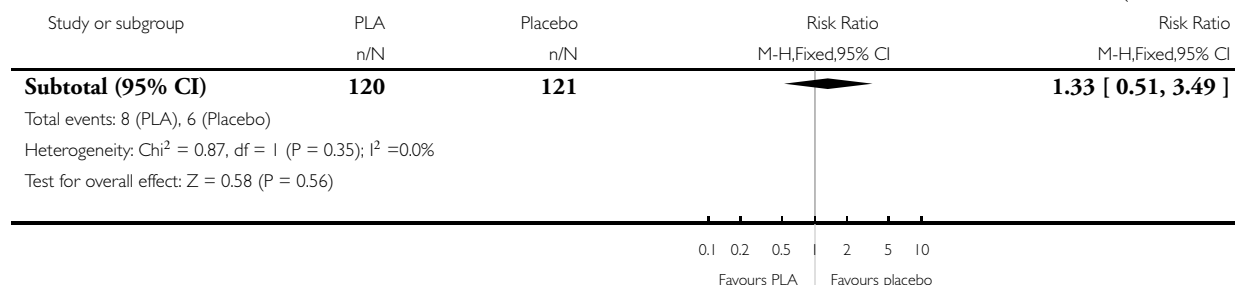
Comparison: 1 Paracervical versus placebo

Outcome: 9 Shoulder pain



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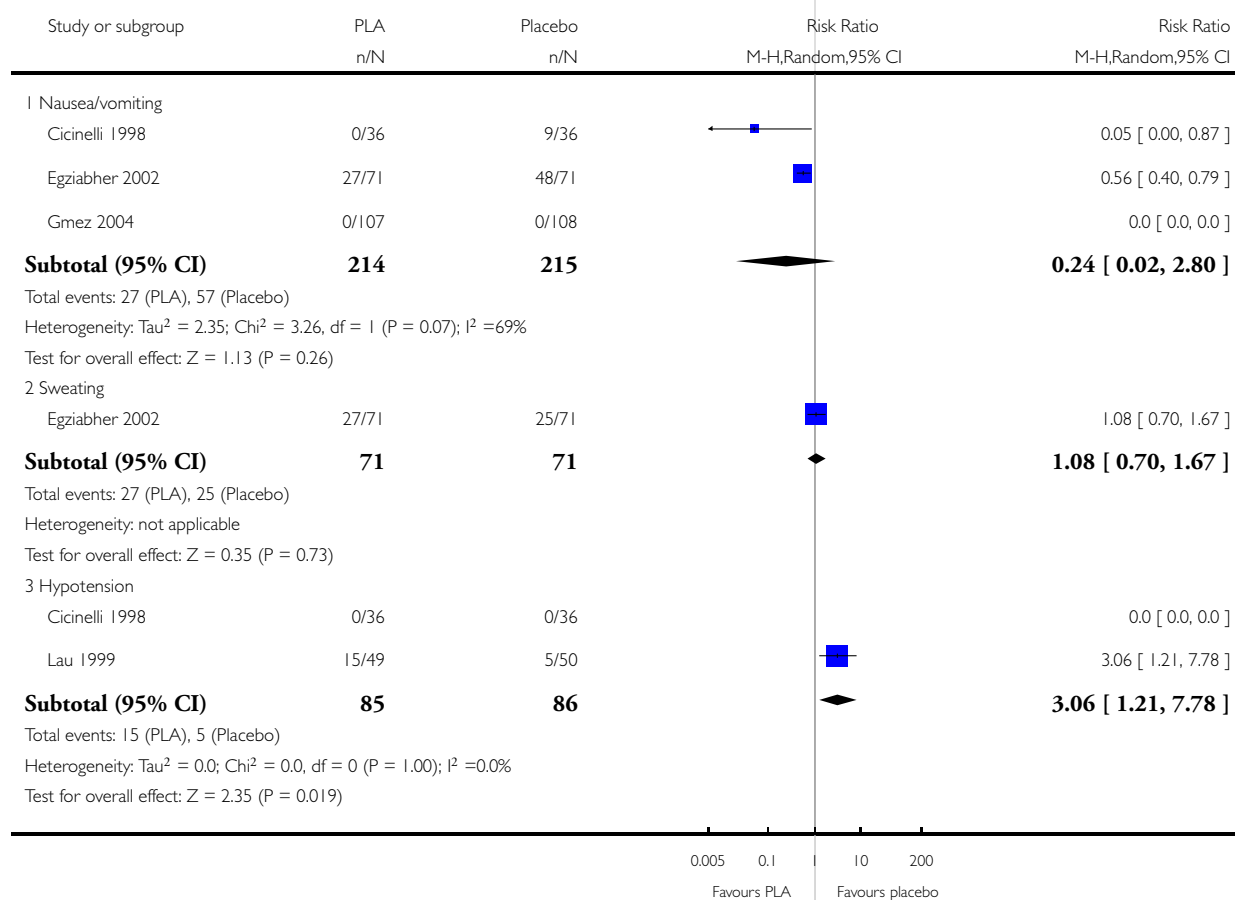


Analysis 1.10. Comparison 1 Paracervical versus placebo, Outcome 10 Adverse effects.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 1 Paracervical versus placebo

Outcome: 10 Adverse effects

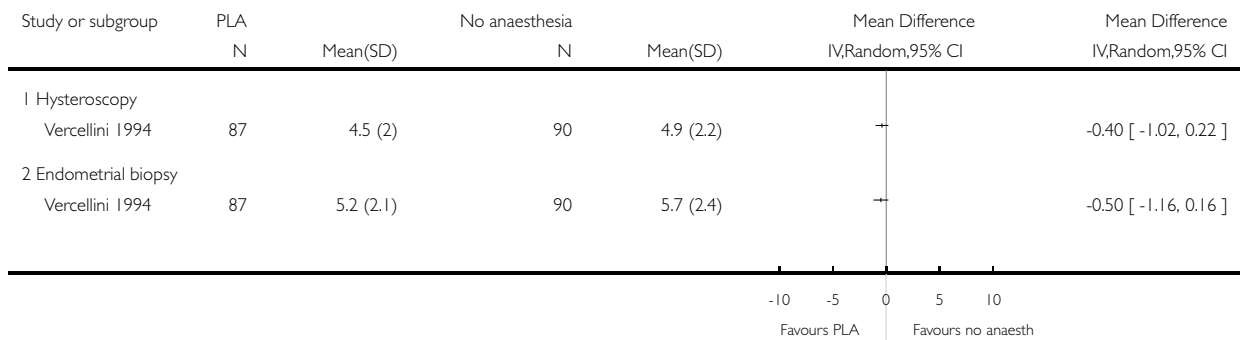


Analysis 2.1. Comparison 2 Paracervical versus no anaesthesia, Outcome 1 Pain during uterine intervention.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 2 Paracervical versus no anaesthesia

Outcome: 1 Pain during uterine intervention

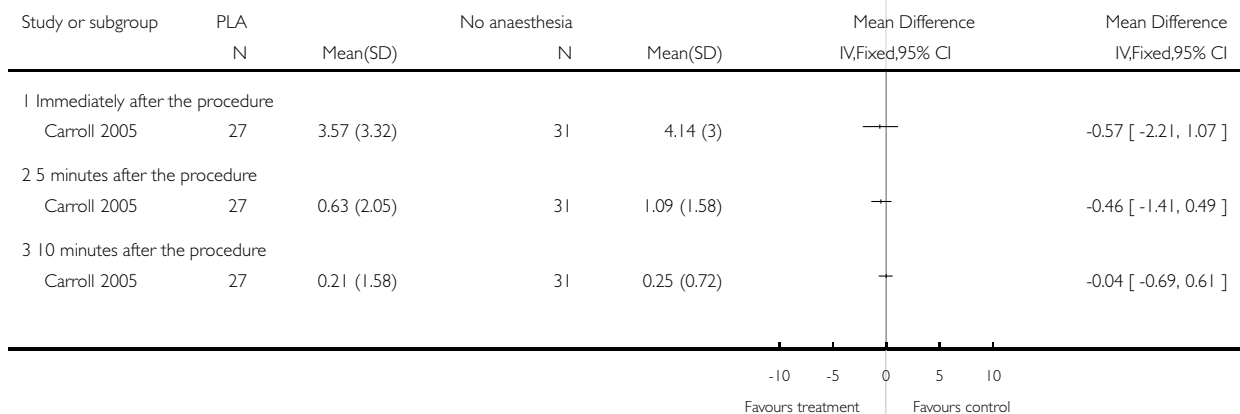


Analysis 2.2. Comparison 2 Paracervical versus no anaesthesia, Outcome 2 Postoperative pain at different times.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 2 Paracervical versus no anaesthesia

Outcome: 2 Postoperative pain at different times

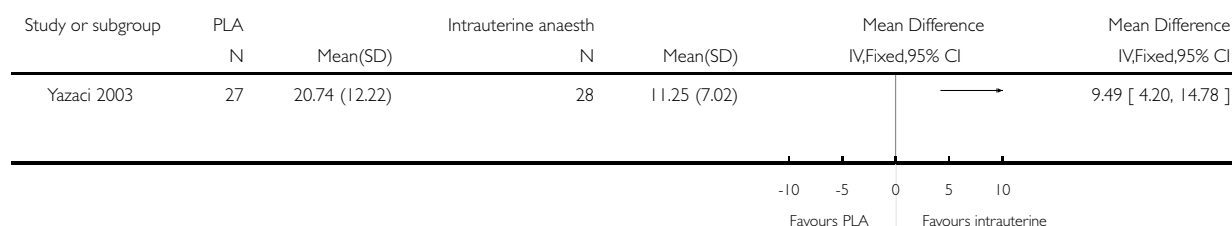


Analysis 3.1. Comparison 3 Paracervical block versus other regional anaesthesia, Outcome 1 Pain during anaesthetic application.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 3 Paracervical block versus other regional anaesthesia

Outcome: 1 Pain during anaesthetic application

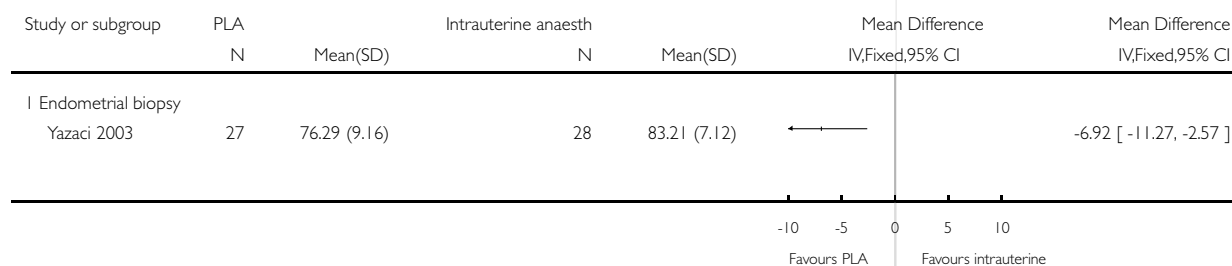


Analysis 3.2. Comparison 3 Paracervical block versus other regional anaesthesia, Outcome 2 Pain during uterine intervention: continuous.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 3 Paracervical block versus other regional anaesthesia

Outcome: 2 Pain during uterine intervention: continuous

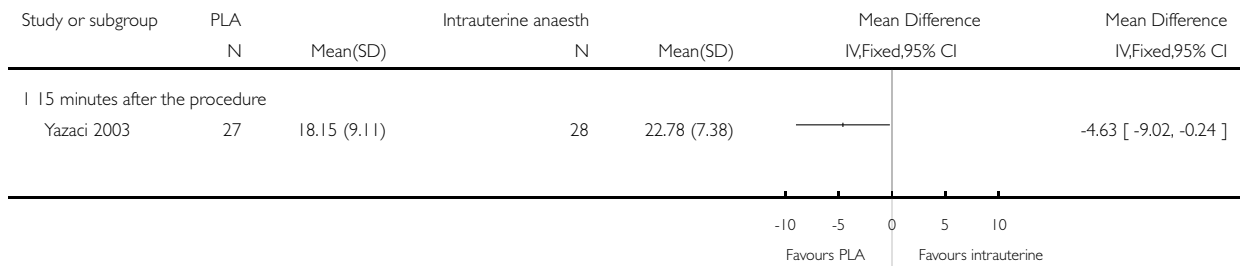


Analysis 3.3. Comparison 3 Paracervical block versus other regional anaesthesia, Outcome 3 Postoperative pain at different time: continuous.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 3 Paracervical block versus other regional anaesthesia

Outcome: 3 Postoperative pain at different time: continuous

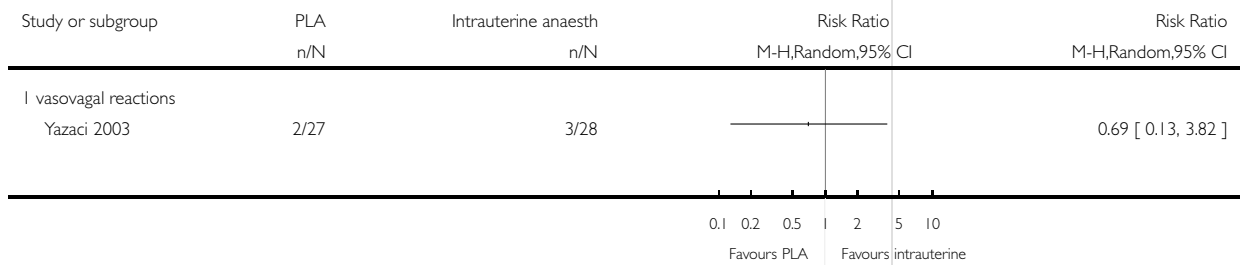


Analysis 3.4. Comparison 3 Paracervical block versus other regional anaesthesia, Outcome 4 Adverse effects.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 3 Paracervical block versus other regional anaesthesia

Outcome: 4 Adverse effects

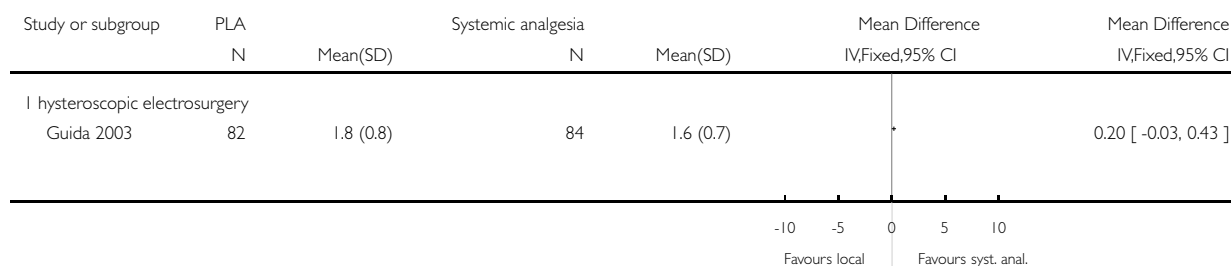


Analysis 4.1. Comparison 4 Paracervical versus systemic analgesia, Outcome 1 Pain during uterine intervention.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 4 Paracervical versus systemic analgesia

Outcome: 1 Pain during uterine intervention

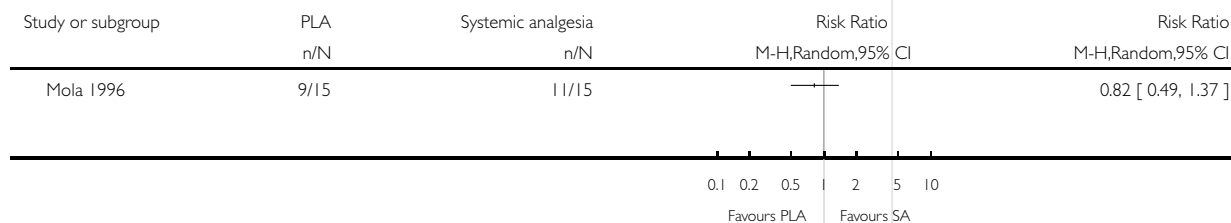


Analysis 4.2. Comparison 4 Paracervical versus systemic analgesia, Outcome 2 Pain during uterine intervention.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 4 Paracervical versus systemic analgesia

Outcome: 2 Pain during uterine intervention

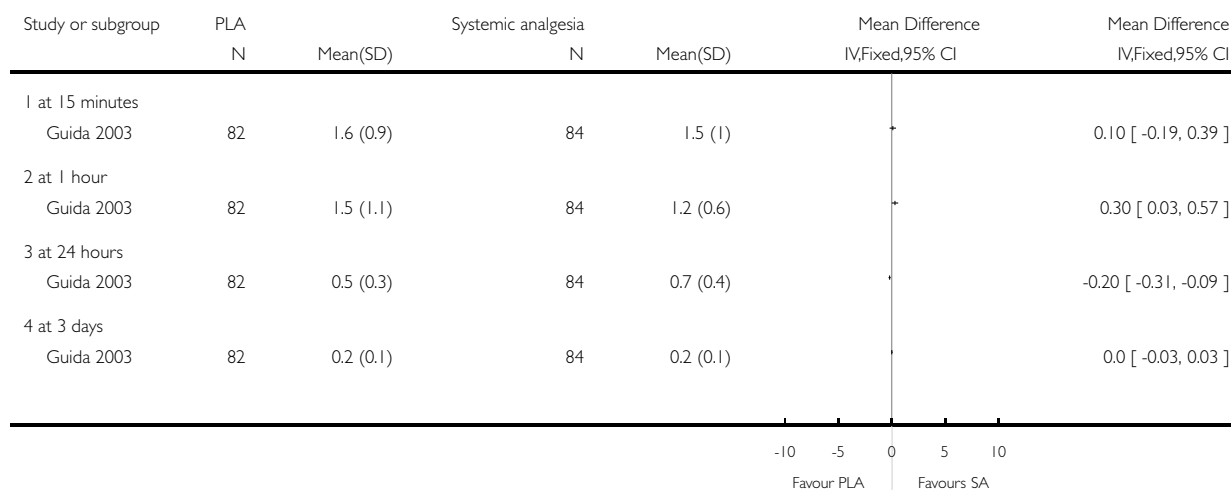


Analysis 4.3. Comparison 4 Paracervical versus systemic analgesia, Outcome 3 Postoperative pain.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 4 Paracervical versus systemic analgesia

Outcome: 3 Postoperative pain

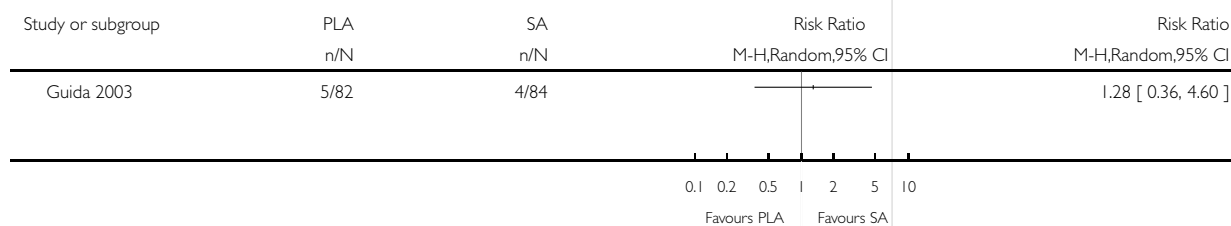


Analysis 4.4. Comparison 4 Paracervical versus systemic analgesia, Outcome 4 Requirement for postoperative analgesics.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 4 Paracervical versus systemic analgesia

Outcome: 4 Requirement for postoperative analgesics

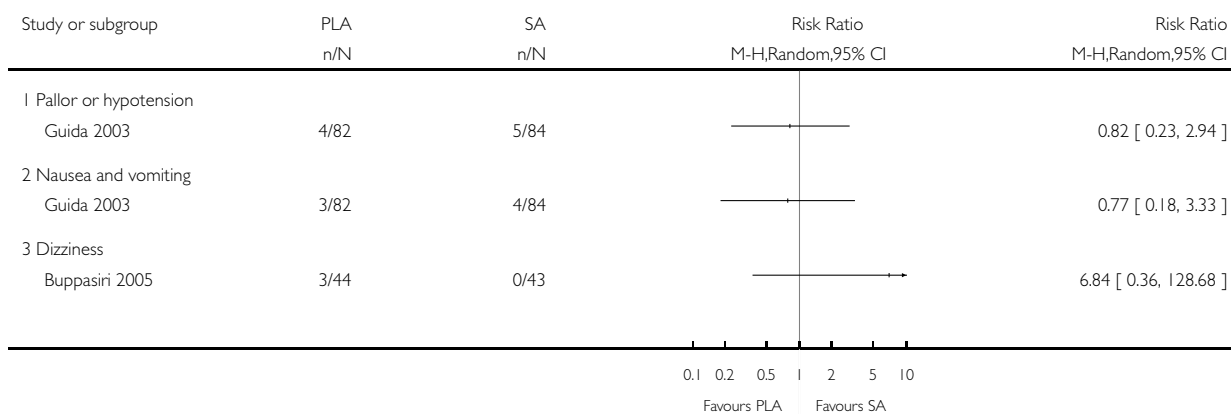


Analysis 4.5. Comparison 4 Paracervical versus systemic analgesia, Outcome 5 Adverse effects.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 4 Paracervical versus systemic analgesia

Outcome: 5 Adverse effects

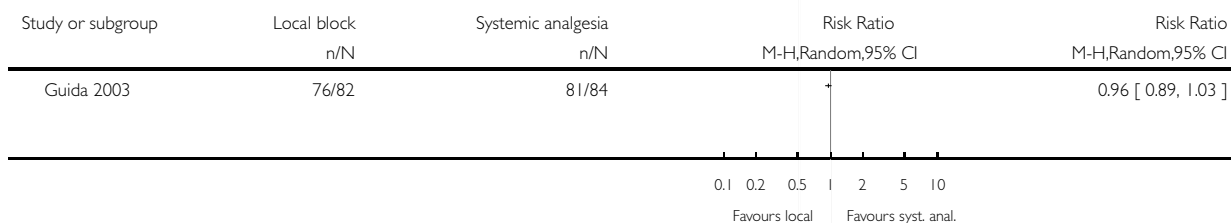


Analysis 4.6. Comparison 4 Paracervical versus systemic analgesia, Outcome 6 Patient satisfaction.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 4 Paracervical versus systemic analgesia

Outcome: 6 Patient satisfaction

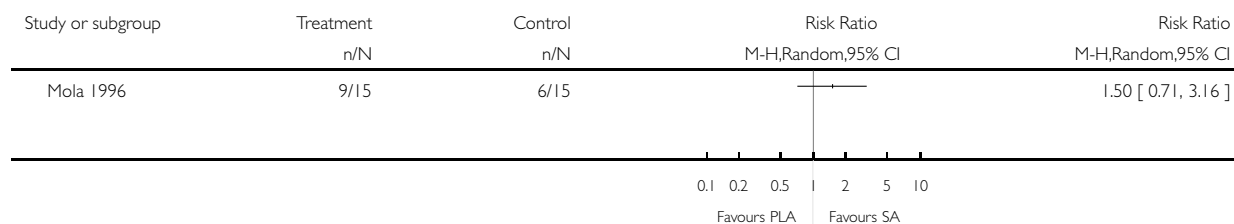


Analysis 4.7. Comparison 4 Paracervical versus systemic analgesia, Outcome 7 Operator's perception of the analgesia.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 4 Paracervical versus systemic analgesia

Outcome: 7 Operator's perception of the analgesia



APPENDICES

Appendix I. CENTRAL search strategy (The Cochrane Library Issue I, 2006)

Number	Search strategy
#1	paracerv*
#2	(paracerv* near (local next anesth*))
#3	(paracervical next block next anesth*)
#4	((paracerv* near block*) or (nerv* near block*))
#5	(lidocain* or lignocain* or bupivacain* or marcain* or levobupivacain* or prilocain* or chlorprocain* or procain* or xylocain* or ropivacain* or tetracain* or amethocain* or mepivacain*)
#6	(#1 or #2 or #3 or #4 or #5)
#7	((obstet* near intervent*)or (gyne* near interven*))
#8	(cervic* near dilat*)
#9	dilat*
#10	(uter* near intervent*)
#11	DILATATION AND CURETTAGE:ME

(Continued)

#12	curett*
#13	(uter* near curett*)
#14	((vacuum and curett*) or (vacuum next extract*) or (vacuum next aspirat*))
#15	(#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14)
#16	(#6 and #15)
#17	PAIN POSTOPERATIVE:ME
#18	POSTOPERATIVE NAUSEA AND VOMITING:ME
#19	(postoperative* near complicat*)
#20	(postoperativ* near pain)
#21	((postoperativ* near nausea) or (postoperativ* near vomit*))
#22	PATIENT SATISFACTION:ME
#23	(patient* near satisfact*)
#24	ABORTION INDUCED:ME
#25	HYPOTENSION ORTHOSTATIC:ME
#26	(#17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25)
#27	(#16 and #26)

Appendix 2. MEDLINE search strategy (1966 to January 2006)

Number	Search strategy
#1	paracerv*
#2	(paracerv* near (local next anesth*))
#3	(paracervical next block next anesth*)
#4	((paracerv* near block*) or (nerv* near block*))

(Continued)

#5	(lidocain* or lignocain* or bupivacain* or marcain* or levobupivacain* or prilocain* or chlorprocain* or procain* or xylocain* or ropivacain* or tetracain* or amethocain* or mepivacain*)
#6	(#1 or #2 or #3 or #4 or #5)
#7	((obstet* near intervent*)or (gyne* near interven*))
#8	(cervic* near dilat*)
#9	dilat*
#10	(uter* near intervent*)
#11	DILATATION AND CURETTAGE:ME
#12	curett*
#13	(uter* near curett*)
#14	((vacuum and curett*) or (vacuum next extract*) or (vacuum next aspirat*))
#15	(#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14)
#16	(#6 and #15)
#17	PAIN POSTOPERATIVE:ME
#18	POSTOPERATIVE NAUSEA AND VOMITING:ME
#19	(postoperative* near complicat*)
#20	(postoperativ* near pain)
#21	((postoperativ* near nausea) or (postoperativ* near vomit*))
#22	PATIENT SATISFACTION:ME
#23	(patient* near satisfact*)
#24	ABORTION INDUCED:ME
#25	HYPOTENSION ORTHOSTATIC:ME
#26	(#17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25)
#27	(#16 and #26)

Appendix 3. EMBASE search strategy (1980 to January 2006)

Number	Search strategy
#1	PARACERV*
#2	Paracerv* near (local an?esth*)
#3	paracervical block an?esth*
#4	explode paracervical-block / all subheadings
#5	explode nerve-block/all subheadings
#6	(paracerv* near block*) or (nerv* near block*)
#7	explode local-anesthetic-agent/all subheadings
#8	explode local-anesthesia/all subheadings
#9	LIDOCAIN* or LIGNOCAIN* or BUPIVACAIN* or MARCAIN* or LEVOBUPIVACAIN* or PRILOCAIN* or CHLORPROCAIN* or PROCAIN* or XYLOCAIN* or ROPIVACAIN* or TETRACAIN* or AMETHOCAIN* or MEPIVACAIN*(56634 records)
#10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#11	(obstet* near intervent*)or (gyn?e* near interven*)
#12	explode uterine-cervix-dilatation/all subheadings
#13	explode obstetric-operation/all subheadings
#14	cervic* near dilat*
#15	dilat*
#16	uter* near intervent*
#17	explode curettage/all subheadings
#18	curett*
#19	uter* near curett*
#20	(vacuum and curett*)or(vacuum extract*) or (vacuum aspirat*)

(Continued)

#21	#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
#22	#10 and #21
#23	explode postoperative complication/all subheadings
#24	post?operative* near complicat*
#25	explode postoperative pain/ all subheadings
#26	post?operativ* near pain
#27	(explode postoperative nausea/ all subheadings) or (explode postoperative vomiting/ all subheadings)
#28	explode postoperative nausea / all subheadings and vomiting
#29	(post?operativ* near nausea) or (post?operativ* near vomit*)
#30	explode patient satisfaction/all subheadings
#31	patient* near satisfact*
#32	explode induced hypotension/all subheadings
#33	explode hypotension/all subheadings
#34	#23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33
#35	#22 and #34

WHAT'S NEW

Last assessed as up-to-date: 30 January 2006.

7 January 2008	Amended	Converted to new review format.
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HISTORY

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Review first published: Issue 1, 2009

CONTRIBUTIONS OF AUTHORS

Conceiving the review: Thumwadee Tangsiriwatthana (TT)

Co-ordinating the review: Ussanee Swadpanich (US)

Undertaking manual searches: TT and US

Screening search results: TT and US

Organizing retrieval of papers: TT

Screening retrieved papers against inclusion criteria: TT, US and Pisake Lumbiganon (PL)

Appraising quality of papers: TT and US

Abstracting data from papers: TT and US

Writing to authors of papers for additional information: TT

Providing additional data about papers: TT

Obtaining and screening data on unpublished studies: TT and US

Data management for the review: TT

Entering data into Review Manager ([Review Manager 5.0](#)): TT

RevMan statistical data: Malinee Laopaiboon (ML)

Other statistical analysis not using RevMan: ML

Double entry of data: (data entered by person one: TT; data entered by person two: US)

Interpretation of data: TT, US and PL

Statistical inferences: ML

Writing the review: TT, US, PL and ML

Securing funding for the review: PL

Performing previous work that was the foundation of the present study: PL

Guarantor for the review (one author): PL

Persons responsible for reading and checking review before submission: TT, US, PL and ML

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Medical Education Centre, Khon Kaen Regional Hospital, Thailand.
- Khon Kaen University, Thailand.

External sources

- Thai Cochrane Network, Thailand.
- Thailand Research Fund (Senior Research Scholar), Thailand.
- Cochrane Anaesthesia Review Group (CARG), Denmark.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed some search strategies from the published protocol for higher sensitivity. See [Appendix 1](#), [Appendix 2](#) and [Appendix 3](#).

INDEX TERMS

Medical Subject Headings (MeSH)

Anesthesia, Local [adverse effects; *methods]; Anesthetics, Local [administration & dosage; adverse effects]; Biopsy [adverse effects]; Dilatation and Curettage [*adverse effects]; Endometrium [pathology]; Hysteroscopy [adverse effects]; Nerve Block [*methods]; Pain [*prevention & control]; Pain, Postoperative [prevention & control]; Randomized Controlled Trials as Topic; Uterus [*surgery]

MeSH check words

Female; Humans; Pregnancy

Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes (Review)

Laopaiboon M, Lumbiganon P, Martis R, Vatanasapt P, Somjaivong B



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Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes (Review)
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[Intervention Review]

Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

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ABSTRACT

Background

Evidence on the benefits of music during caesarean section under regional anaesthesia to improve clinical and psychological outcomes for mothers and infants has not been established.

Objectives

To evaluate the effectiveness of music during caesarean section under regional anaesthesia for improving clinical and psychological outcomes for mothers and infants.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 September 2008).

Selection criteria

We included randomised controlled trials comparing music added to standard care during caesarean section under regional anaesthesia to standard care alone.

Data collection and analysis

Two review authors, Malinee Laopaiboon and Ruth Martis, independently assessed eligibility, risk of bias in included trials and extracted data. We analysed continuous outcomes using a mean difference (MD) with a 95% confidence interval (CI).

Main results

One trial involving 76 women who planned to have their babies delivered by caesarean section met the inclusion criteria, but data were available for only 64 women. This trial was of low quality with unclear allocation concealment and only a few main clinical outcomes reported for the women. The trial did not report any infant outcomes. It appears that music added to standard care during caesarean

section under regional anaesthesia had some impact on pulse rate at the end of maternal contact with the neonate in the intra-operative period (MD -7.50 fewer beats per minute, 95% CI -14.08 to -0.92) and after completion of skin suture for the caesarean section (MD -7.37 fewer beats per minute, 95% CI -13.37 to -1.37). There was also an improvement in the birth satisfaction score (maximum possible score of 35) (MD of 3.38, 95%CI 1.59 to 5.17). Effects on other outcomes were either not significant or not reported in the one included trial.

Authors' conclusions

The findings indicate that music during planned caesarean section under regional anaesthesia may improve pulse rate and birth satisfaction score. However, the magnitude of these benefits is small and the methodological quality of the one included trial is questionable. Therefore, the clinical significance of music is unclear. More research is needed to investigate the effects of music during caesarean section under regional anaesthesia on both maternal and infant outcomes, in various ethnic pregnant women, and with adequate sample sizes.

PLAIN LANGUAGE SUMMARY

Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Caesarean section is a surgical procedure for delivering a baby. It involves making surgical incisions into the mother's abdominal wall and uterus. These operations are performed if there is a serious medical concern for the mother or baby. Caesarean sections are generally done with regional anaesthesia, either a spinal or epidural block with anaesthetic injected into the area around the spine in the lower back, which makes the mother feel numb from the waist down. Women have increased risks associated with anaesthesia and surgery, and the baby may be more likely to be admitted to a neonatal unit or separated from the mother.

Women having a caesarean section under regional anaesthesia are often highly anxious during the operation and may feel some discomfort. Listening to relaxing music of the woman's choice may lead to better outcomes and less need for treatment.

The review findings indicate that listening to music during planned caesarean section under regional anaesthesia may improve pulse rates and birth satisfaction scores, although the effect sizes were not large enough to indicate a clinically beneficial effect. The review authors identified one controlled trial that randomly assigned 76 women who listened to their preferred music through earphones, or to standard care, but data were available for only 64 women. The music was provided from the beginning of anaesthesia to the end of surgery. The women's heart rates were reduced by some seven beats/minute when measured at the end of contact with the newborn during the intra-operative period and after the surgeon had completed skin suture. Birth satisfaction scores were increased by a mean of 3.4 points on a 35-point scale when women listened to music. Respiration rates were no different for the two groups and neither were levels of anxiety, which decreased at the end of contact with the newborn and again after closing the skin, with no clear difference with or without music. The trial was from Taiwan and reporting of trial methodology was poor.

BACKGROUND

Caesarean section is a surgical procedure for delivering a baby through incisions made on the mother's abdominal wall and uterus. Caesarean section is performed for emergency conditions, for example, for fetal distress and cephalopelvic disproportion. It is also electively performed for non-emergencies, e.g. previous caesarean section, breech presentation. Pregnant mothers undergoing caesarean section often experience anxiety in anticipation of the event that may be unfamiliar, uncomfortable or have undesirable results. This anxiety can increase the risk of psychological and physiological complications and delays in postoperative recovery (Good 1996; Mok 2003). This anxiety, however, could be reduced

by various means including support by their surgeons, nurses and, possibly, music in the operative rooms.

There is evidence to suggest that there are increased maternal risks associated with surgery, including anaesthetic risks, surgical complications, increased blood loss, need for transfusion, and pulmonary embolism (Kelleher 1994). Women may also experience restrictions in their daily activities (Chippington 2004) and experience breastfeeding difficulties (Francome 1993). Caesarean section may also increase the chances of women experiencing problems in subsequent pregnancies related to uterine scarring (Hemminki 1996). Furthermore, new, unexpected, long-term risks of caesarean section continue to be reported; these include abnor-

mal placentation (Wu 2005), ectopic pregnancy, haemorrhage and hysterectomy following uterine evacuation, latex allergy, implantation endometriosis, adenomyosis and increased hospital readmission (Bewley 2002). Caesarean section has also been associated with emotional difficulties (Clement 2001) for the woman, including postpartum depression and negative feelings about the experience of childbirth (Minkoff 2003). Suggested increased risks for babies delivered by caesarean section include increased rates of admission to neonatal units and separation of the mother and neonate (Treffers 1993), iatrogenic prematurity (Wagner 2000), laceration (Smith 1997), increased neonatal respiratory problems (Madar 1999) and stillbirth if the mother has previously had a caesarean section (Smith 2003).

Music is an intentional auditory stimulus with organised elements including melody, rhythm, harmony, timbre, form, and style. Repetitive listening allows the listener to identify and predict sounds (Standley 2002). Thus, repeated exposure may enhance clinical effects (Kemper 2005). An observational study (Good 2000) found that musical choices were related to cultural background of patients admitted to hospitals. Music was found to enhance well being in a randomised crossover trial (McCrary 1998). Other studies report that music reduced stress and distracted adult hospital patients from unpleasant symptoms (in a systematic review of RCTs by Evans 2002 and also in a quasi-experimental study by Shertzer 2001). Although there are wide variations in individual preferences, music appears to exert direct physiologic effects through the autonomic nervous system. For example, one randomised trial in which outcomes were measured repeatedly (White 1999) and two quasi-intervention studies (Umemura 1998; Urakawa 2005) report that listening to classical music may increase the heart rate variability, whereas listening to noise or rock music may decrease heart rate variability (reflecting greater stress) in healthy subjects. Music has also been found to have indirect effects by modifying caregiver behaviour. A randomised controlled trial (RCT) (Lepage 2001) and two quasi-intervention studies (Haun 2001; Yung 2002) found that music effectively reduced anxiety and improved the mood of medical and surgical patients, patients in intensive care units and patients undergoing procedures. Music is a low-cost intervention that may reduce surgical, procedural, acute, and chronic pain. However, the findings are from many studies that have methodological problems, such as small sample sizes, lack of randomisation, and lack of control for patient anaesthesia (Kemper 2005). Furthermore, a systematic review of RCTs on music for pain relief (Cepeda 2006) found that the beneficial effect of music on pain intensity levels and opioid requirements was unclear.

Other studies have found that music improved the quality of life for patients receiving palliative care (Hilliard 2003), enhancing a sense of comfort and relaxation according to results from a pre and post study (Burns 2001) and two RCTs (Cassileth 2003; Smith 2001). A quasi-intervention study (Allen 1994) and another RCT

(Bittman 2003) show that providing music to caregivers may be a cost-effective and enjoyable strategy to improve empathy, compassion, and relationship-centred care while not increasing errors or interfering with the technical aspects of care.

Music's ability to slow respiratory rates and decrease the stress response appears to be beneficial during labour. It has been reported that music shortened labour in an observational study (Winokur 1984). Even when the course of labour does not speed up when music is utilised, the perceived length of labour decreases, as shown in a quasi-intervention study (Clark 1981). A review by McKinney 1990 and a self-controlled experiment by Hanser 1983 have both found that when music is played, pain is decreased.

The efficacy of music for premature infants was reported in a nonsystematic review of literature by Standley 2002, and their findings suggest that music is clinically useful for the care of this group. One cohort study describes the use of medical resonant music as preoperative preparation for caesarean section. Music is thought to influence cortical dynamics and through it subcortical and vegetative areas of the nervous system (Wein 1997). Such influence is thought to cause an integration and synchronisation of different activity systems within the human body, strengthening psycho-physiological defences and improving health conditions (Gerasimovich 1995; Gerasimovich 1999). Compared with a control group of women who received sedatives for preoperative preparation, the intervention group receiving Medical Resonance Therapy music (MRT-music) had lower cortisol levels and noted better sleep and less need for analgesics postoperatively (Sidorenko 2000).

Most caesarean sections are performed under epidural or spinal block where the pregnant woman is anaesthetised from the waist down. However, there is often some degree of discomfort for the woman before the baby is born, when the uterus is manipulated. Music may be useful during caesarean section under regional anaesthesia in terms of improving outcomes for the mother and baby but thus far there has not been a systematic review on this topic.

OBJECTIVES

To assess the effectiveness of music during caesarean section under regional anaesthesia for improving clinical and psychological outcomes for mothers and infants.

METHODS

Criteria for considering studies for this review

Types of studies

All identified published, unpublished and ongoing RCTs and quasi-RCTs for inclusion. The randomised units could be individual or clustered (e.g. hospitals).

Types of participants

Pregnant women scheduled to receive caesarean sections under regional anaesthesia.

Types of interventions

The addition of any type of music to routine care compared with routine care alone during caesarean section.

Types of outcome measures

Primary outcomes

For mothers

1. Pain intensity (self-report measured with the visual analogue scale during and after caesarean section)
2. Analgesic requirement during and after caesarean section
3. Anxiety during and after caesarean section as defined by investigators
4. Maternal death
5. Clinical outcomes
 - 5.1 Blood pressure
 - 5.2 Pulse haemoglobin oxygen saturation (SpO₂)
 - 5.3 Respiratory rates
 - 5.4 Heart rate and its variability
 - 5.5 Blood loss
 - 5.6 Immediate postoperative complications

For infants

6. Apgar scores at one and five minutes
7. Birth asphyxia
8. Infant death

Secondary outcomes

For mothers

1. Maternal satisfaction
2. Injury from surgical procedures such as urinary bladder injury, vessel injury, etc
3. Skin to skin contact between mother and infant during or after caesarean section
4. Breastfeeding initiation and duration

For infants

5. Injury from surgical procedures such as cut wound, etc
6. Physical and psychological development of infants as defined by investigators

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 (30 September 2008).

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. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, 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

Selection of studies

Two review authors, Malinee Laopaiboon (ML) and Ruth Martis (RM), independently assessed for inclusion all potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion with the third review author, Pisake Lumbiganon (PL).

Assessment of methodological quality of included studies

Malinee Laopaiboon (ML) and Ruth Martis (RM) independently assessed risk of bias for the included study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2008](#)).

1) Sequence generation (checking for possible selection bias)

We described for the 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:

- yes, low risk of bias (any truly random process e.g. random number table; computer random number generator);
- no, high risk of bias (any non random process e.g. odd or even date of birth); or
- unclear.

2) Allocation concealment (checking for possible selection bias)

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

We assessed the methods as:

- yes, low risk of bias (e.g. consecutively numbered sealed opaque envelopes);
- no, high risk of bias (open random allocation; unsealed or non-opaque envelopes); or
- unclear.

3) Blinding (checking for assessment bias)

It was not feasible to blind clinicians and participants to the music. We only assessed blinding for outcome assessors:

- yes, low risk of bias;
- no, high risk of bias; or
- unclear for outcome assessors.

4) Incomplete outcome data (checking for possible attrition bias)

We describe for the included study, and for each outcome, the completeness of data including attrition and exclusions from the analysis. We addressed whether attrition and exclusions were reported, the numbers included in the analysis 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.

We assessed methods as:

- yes, low risk of bias;
- no, high risk of bias; or
- unclear.

5) Selective reporting bias

We described the possibility of selective outcome reporting bias.

We assessed the methods as:

- yes, 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);
- no, 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 were expected to be reported); or
- unclear.

6) Other sources of bias

We described any important concerns about other possible sources of bias in the one included study.

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

- yes, low risk of bias;
- no, high risk of bias; or
- unclear.

We made explicit judgements about whether the included study was at high risk of bias, low risk of bias or unclear risk of bias according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008).

Data extraction and management

We designed a form, based on the Cochrane Pregnancy and Childbirth Group's template, to extract data. ML and RM extracted the data using the agreed form. We resolved discrepancies through discussion. We used the Review Manager software (RevMan 2008) to double enter all the data or a sub sample.

We did not contact authors of the original report as we had sufficient information.

Data analysis

This review included one trial. We have provided full methods of data analysis for future updates of this review in [Appendix 1](#).

Measures of treatment effect

We carried out statistical analysis using Review Manager software (RevMan 2008). We have reported continuous outcomes such as maternal blood pressure, pain and infant Apgar scores as mean differences with 95% confidence intervals (CI) if the outcomes are measured in the same way among trials.

RESULTS

Description of studies

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

The search strategy identified two potentially relevant studies. We excluded one ([Reza 2007](#)) because the caesarean section was done under general anaesthesia (see '[Characteristics of excluded studies](#)').

We included one RCT in this review ([Chang 2005](#)). For more information see '[Characteristics of included studies](#)'. The trial was undertaken in a medical centre in southern Taiwan between June and October 2002, and evaluated the effects of music on women's clinical and psychological measures, such as anxiety and satisfaction during caesarean section. Seventy-six women, scheduled to deliver their babies by caesarean section, were eligible following initial assessment and allocation. Thirty-eight women were each randomly assigned to either the intervention (music added to standard care) or the control group (standard care alone). Consent to receive music was given after random allocation. There were six women in the intervention group who declined participation for various reasons: two lost interest; two received sedative/nitrous oxide; one had a newborn with imperforate anus; and one had failure of local anaesthesia. Six women participating in the control group dropped out for the following reasons: two had an emergency caesarean section; and four received sedative/nitrous oxide. In total, 64 randomised women were studied, with 32 each in

the intervention and control groups. For the intervention group, women received standard care plus listening to music through earphones using a compact disc player. Women chose their preferred music from either western classical, new age or Chinese religious music. Music listening started from the beginning of anaesthesia to the end of surgery, and lasted at least 30 minutes. Mean listening time was 87.59 minutes (SD 13.01). For the control group, women received standard care without music. The trial reported the women's self-assessed anxiety (measured using the Visual Analogue Scale for Anxiety (VASA), which consists of a 10 cm horizontal line with the descriptors 'no anxiety' at the left extent and 'worst possible anxiety' at the right extent ([Gift 1989](#))). Clinical measures reported by [Chang 2005](#) include: pulse haemoglobin oxygen saturation (SpO₂ (%)); finger temperature (° F); respiration rate (per minute); pulse rates (beats/minute); systolic blood pressure (mmHg); and diastolic blood pressure (mmHg).

Data was collected at three points: in the operation room prior to anaesthesia and caesarean section (pre-test); at the end of maternal contact with the neonate in the intra-operation period (post-test I); and after completion of skin suture for the caesarean section (post-test II). The trial also reported the women's birth satisfaction, as assessed by the Satisfaction of Caesarean Delivery Scale (SCDS) and measured at the post-test II period only. The SCDS was designed specifically for the study; for more information about this instrument see [Characteristics of included studies](#). The baseline characteristics of the two groups are given in [Table 1](#).

Table 1. Outcomes measured at pre-test

Outcomes	Intervention	Control
	Mean (SD)	Mean (SD)
SpO ₂ (%)	99.22 (0.94)	98.88 (1.41)
Respiration rate (per minute)	22.72 (2.25)	23.34 (2.66)
Pulse rate (beats/minute)	86.69 (13.65)	90.25 (10.65)
Systolic blood pressure (mm Hg)	131.72 (18.03)	126.16 (15.90)
Diastolic blood pressure (mm Hg)	80.34 (15.85)	77.00 (12.86)
Anxiety (VASA) scores	6.80 (3.05)	5.54 (3.42)

Risk of bias in included studies

The one included trial was assessed as having 'unclear' information in five domains of risk of bias: sequence generation; allocation concealment; blinding; free selective reporting; and free other risk of bias. Women eligible for inclusion were sequentially recruited and then randomly allocated to the intervention or control groups.

It was not feasible to blind the participants and clinicians to music. Outcome assessors for VASA scores and birth satisfaction were not blinded because the outcomes were self assessed by the participants themselves. However, the trial does not report on blinding of outcome assessors for clinical outcomes. The analysis was not done on an intention-to-treat basis because 12 patients (six in the intervention group and six in the control group) were excluded

after randomisation. Outcomes were measured from a total of 64 women: 32 women in the intervention group and 32 women in the control group. Selective outcome reporting cannot be ruled out because the trial protocol was not available to compare the planned outcomes with those reported.

Effects of interventions

One trial (Chang 2005) of 64 women (32 for music group and 32 for control group) evaluated the effects of music on women's clinical outcomes, anxiety and satisfaction during caesarean section.

Primary outcomes

The clinical outcomes of SpO₂, respiration rate, pulse rates, systolic and diastolic blood pressure, and VASA anxiety score were presented as means and standard deviations (SD) for the intervention and control groups at two time points after the intervention. Mean difference (MD) percentages of SpO₂ were 0.03 (95% CI -0.27 to 0.33) at the end of maternal contact with the neonate in the intra-operation period and -0.31 (95% CI -0.75 to 0.13) after completion of skin suture for the caesarean section (See Analysis 1.1; Analysis 1.2).

Small, non-significant changes in respiration rates for both groups were seen at the two post-test points. MD were not statistically significant, -0.82 (95% CI -1.70 to 0.06), at the end of maternal contact with the neonate in the intra-operation period and -0.53 (95% CI -1.27 to 0.21) after completion of skin suture for the caesarean section (See Analysis 1.3; Analysis 1.4).

Reductions in pulse rates at the two post-test periods were larger in the intervention group compared to the control group. MD were statistically significant, -7.50 (95% CI -14.08 to -0.92) at the end of maternal contact with the neonate in the intra-operation period and -7.37 (95% CI -13.37 to -1.37) after completion of skin suture for the caesarean section (See Analysis 1.5; Analysis 1.6).

No changes in systolic blood pressure were seen at the two post-test periods for the women in the intervention group compared with those in the control group. MDs of systolic blood pressures were not statistically significant, -1.66 mmHg (95% CI -7.30 to 3.98), at the end of maternal contact with the neonate in the intra-operation period and 0.90 mmHg (95% CI -5.76 to 7.56) after completion of skin suture for the caesarean section (See Analysis 1.7; Analysis 1.8).

There were no significant changes in the patterns of diastolic blood pressure in women in the intervention and the control groups, at the end of maternal contact with the neonate in the intra-operation period (MD -1.36; 95% CI -7.88 to 5.16) or after completion of skin suture for the caesarean section (MD -0.09; 95% CI -5.00 to 4.82) (See Analysis 1.9; Analysis 1.10).

Chang 2005 reports that the mean anxiety (VASA) scores were decreased ($P < 0.01$) between pre- and post-test in both the intervention and control groups. At both time points (post-test I and II) there was no evidence of a statistically significant difference between groups (Analysis 1.12; Analysis 1.13)

Secondary outcomes

Birth satisfaction scores were statistically significantly higher in the intervention group compared with the control group (MD 3.38, 95% CI 1.59 to 5.17) (See Analysis 1.11).

DISCUSSION

This review aimed to assess the effectiveness of music during caesarean section under regional anaesthesia for improving clinical and psychological outcomes for mothers and infants.

We included only one trial (Chang 2005) involving 64 of 78 randomised women. Outcomes included SpO₂, respiration rates, pulse rates, systolic and diastolic blood pressure, and VASA anxiety score as primary outcomes and birth satisfaction as a secondary outcome. There were no statistically significant differences between the intervention and control groups for most outcomes. There were statistically significant differences between the intervention and control groups for pulse rates and birth satisfaction. However, the effect sizes were small and may not suggest a clinically beneficial effect of music. Although the mean VASA scores were lower in the intervention group than in the control group at the two post-test periods, the data are skewed, so statistically significant differences cannot be ruled out.

The included trial may be of limited generalisability to clinical practice. The trial was conducted in Taiwan, with data from only 64 women available for inclusion in the final analysis. Three types of music (Western classical, new age and Chinese religious) might have different effects on outcomes. The number of women choosing each type of music was not available. We, therefore, cannot rule out differential effects on maternal outcomes resulting from the type of music. The maternal outcomes were limited to anxiety, some clinical outcomes and birth satisfaction. No infant outcomes were reported. The reporting of trial methodology was poor and there was no information available in relation to randomisation methods and allocation concealment. In this included study it was not possible to blind the assessors, as it would have been obvious which women were in the receiving music therapy (the intervention group) because they were wearing earphones connected to a compact disc player. In addition, risk of attrition bias (drop-out) was possible since 12 patients were excluded after randomisation. These factors limit the methodological strength of the evidence.

AUTHORS' CONCLUSIONS

Implications for practice

The findings of this review indicate that music during caesarean section under regional anaesthesia may have positive effects on pulse rates and birth satisfaction of mothers. However, the poor

methodological quality of the one included study makes it impossible to draw any firm conclusions about the effectiveness of music during caesarean section under regional anaesthesia for improving maternal and infant outcomes.

Implications for research

More research is needed in order to evaluate the effects of music during caesarean section under regional anaesthesia. Future RCTs with good methodology, in terms of randomisation methods, concealment, and blinded outcome assessors, should be undertaken involving different types of music, adequate sample sizes, and pregnant women from a variety of different ethnic groups.

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), one or more members of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser. Thanks also to Philippa Middleton for her kind suggestions on our draft review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Chang 2005

Methods	RCT, reported only sequentially recruited eligible women which were then randomly allocated to intervention and control groups. Blinding: assessment of some outcomes, i.e. anxiety and birth satisfaction were not blinded. Description of withdrawals: yes, 12 women (six in the intervention and six in the control) dropped out after randomisation for various reasons. Intention-to-treat analysis: no.
Participants	76 women scheduled to receive caesarean section between June and October 2002 at a medical centre in southern Taiwan. Participants were married, aged 20-40 years, term pregnancies and planned to undergo caesarean births, underwent spinal or epidural anaesthesia, and having singleton babies with Apgar scores ≥ 7 at 5 minutes. Number of women randomised: 76, but only 64 (32 for the intervention (music) group and 32 for the control group) received interventions for the following reasons: Intervention group: 6 declined to participate (2 lost interest, 2 received sedative/nitrous oxide, 1 had a newborn with imperforate anus and 1 had failure of local anaesthesia). Control group: 6 dropped out (2 had emergency caesarean section and 4 received sedative/nitrous oxide).
Interventions	Intervention group: standard care plus at least 30 minutes listening to music through earphones via a compact disc player. Participants chose the music they preferred: either Western classical, new age, or Chinese religious music. Music listening started at the beginning of anaesthesia until the end of surgery. The researcher accompanied participant into theatre and stayed to obtain data. Control group: received standard care and no music. The researcher accompanied participant into theatre and stayed to obtain data.
Outcomes	Primary: anxiety in VASA consisting of a 10 cm horizontal line with the descriptors 'no anxiety' at the left and 'worst possible anxiety' at the right. clinical outcomes: SpO₂, temperature of finger, respiration rate, pulse rates, systolic blood pressure, diastolic blood pressure, all measured by standard tests without the assessor's knowledge. Secondary: birth satisfaction: women's satisfaction of caesarean section delivery scale (SCDS) designed for the study. The SCDS was composed of seven items, including the woman's perceived health status, the perceived health status of the baby, the maintenance of physical function, the maintenance of physical comfort, seeking safe passage for herself, ego orientation, and birth atmosphere.

Chang 2005 (Continued)

	Items are scored on a Likert-type scale of 1 to 5, representing 1, extremely dissatisfied; 2, not satisfied; 3,uncertain; 4, satisfied; and 5, extremely satisfied. Data were collected at three points: pre-test: at the operation room prior to anaesthesia and caesarean section; post-test I: upon the end of maternal contact with the neonate in the intra-operation period; post-test II: after completion of skin suture for the caesarean section. Data on birth satisfaction were collected only at the post-test II period.	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No description.
Allocation concealment?	Unclear	Reported as “sequentially recruited eligible women then randomly allocated to intervention and control”.
Blinding? All outcomes	Unclear	Not feasible to blind participants and clinicians. No information given regarding the assessors for clinical outcomes. Self assessment by participants for VASA scores and birth satisfaction but were recorded to data sheets by the researcher.
Incomplete outcome data addressed? All outcomes	Yes	Outcomes were able to be measured in the total 64 women being received intervention (32) and control (32).
Free of selective reporting?	Unclear	The trial protocol was not available to compare the planned outcomes with reported outcomes.
Free of other bias?	Unclear	No other information given in the paper.

SpO2: pulse haemoglobin oxygen saturation

VASA: Visual Analogue Scale for Anxiety

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

Reza 2007	Caesarean section was done under general anaesthesia, which does not comply with our inclusion criteria of caesarean sections under regional anaesthesia.
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DATA AND ANALYSES

Comparison 1. Music added to standard care (intervention) versus standard care alone (control)

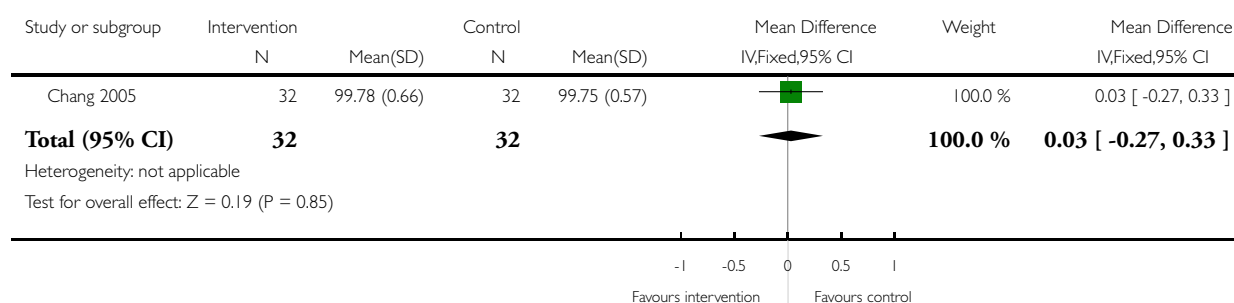
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SpO ₂ at post-test I	1	64	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.27, 0.33]
2 SpO ₂ at post-test II	1	64	Mean Difference (IV, Fixed, 95% CI)	-0.31 [-0.75, 0.13]
3 Respiration rate at post-test I	1	64	Mean Difference (IV, Fixed, 95% CI)	-0.82 [-1.70, 0.06]
4 Respiration rate at post-test II	1	64	Mean Difference (IV, Fixed, 95% CI)	-0.53 [-1.27, 0.21]
5 Pulse rate at post-test I	1	64	Mean Difference (IV, Fixed, 95% CI)	-7.5 [-14.08, -0.92]
6 Pulse rate at post-test II	1	64	Mean Difference (IV, Fixed, 95% CI)	-7.37 [-13.37, -1.37]
7 Systolic blood pressure at post-test I	1	64	Mean Difference (IV, Fixed, 95% CI)	-1.66 [-7.30, 3.98]
8 Systolic blood pressure at post-test-II	1	64	Mean Difference (IV, Fixed, 95% CI)	0.90 [-5.76, 7.56]
9 Diastolic blood pressure at post-test I	1	64	Mean Difference (IV, Fixed, 95% CI)	-1.36 [-7.88, 5.16]
10 Diastolic blood pressure at post-test II	1	64	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-3.00, 4.82]
11 Birth satisfaction at post-test II	1	64	Mean Difference (IV, Fixed, 95% CI)	3.38 [1.59, 5.17]
12 Anxiety (VASA) score post-test I	1	64	Mean Difference (IV, Fixed, 95% CI)	-1.11 [-2.49, 0.27]
13 Anxiety (VASA) score post-test II	1	64	Mean Difference (IV, Fixed, 95% CI)	-0.78 [-1.90, 0.34]

Analysis 1.1. Comparison 1 Music added to standard care (intervention) versus standard care alone (control), Outcome 1 SpO₂ at post-test I.

Review: Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Comparison: 1 Music added to standard care (intervention) versus standard care alone (control)

Outcome: 1 SpO₂ at post-test I

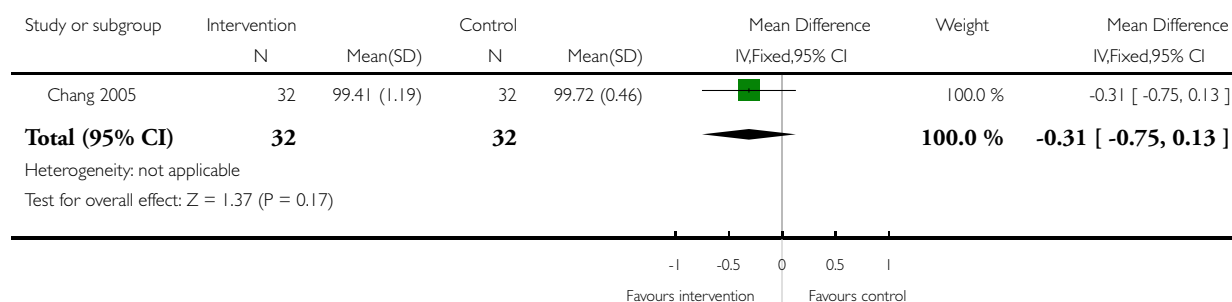


Analysis 1.2. Comparison 1 Music added to standard care (intervention) versus standard care alone (control), Outcome 2 SpO₂ at post-test II.

Review: Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Comparison: 1 Music added to standard care (intervention) versus standard care alone (control)

Outcome: 2 SpO₂ at post-test II

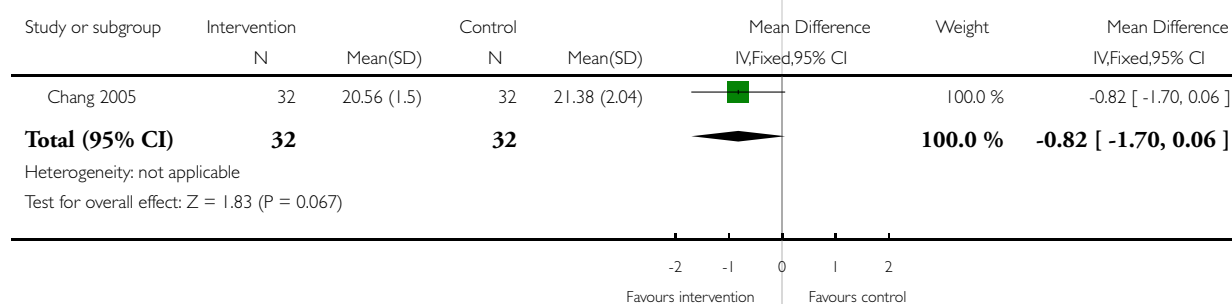


Analysis 1.3. Comparison 1 Music added to standard care (intervention) versus standard care alone (control), Outcome 3 Respiration rate at post-test I.

Review: Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Comparison: 1 Music added to standard care (intervention) versus standard care alone (control)

Outcome: 3 Respiration rate at post-test I

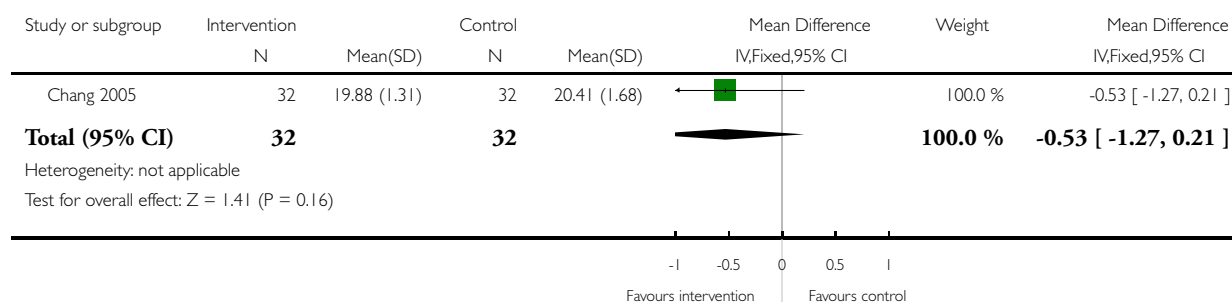


Analysis 1.4. Comparison I Music added to standard care (intervention) versus standard care alone (control), Outcome 4 Respiration rate at post-test II.

Review: Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Comparison: I Music added to standard care (intervention) versus standard care alone (control)

Outcome: 4 Respiration rate at post-test II

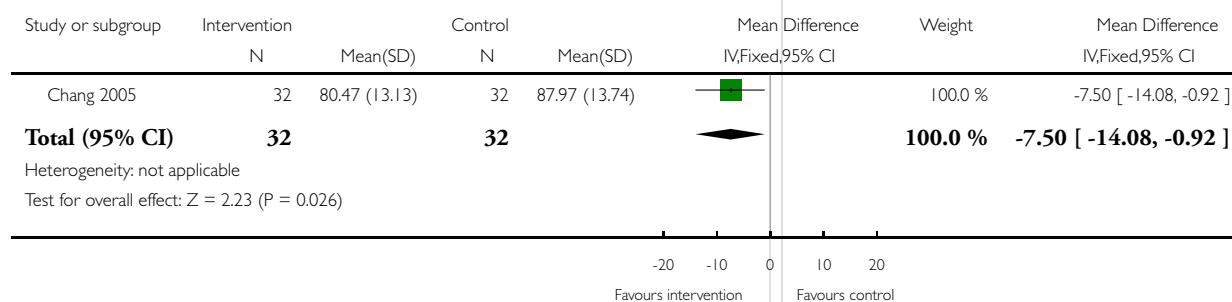


Analysis 1.5. Comparison I Music added to standard care (intervention) versus standard care alone (control), Outcome 5 Pulse rate at post-test I.

Review: Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Comparison: I Music added to standard care (intervention) versus standard care alone (control)

Outcome: 5 Pulse rate at post-test I

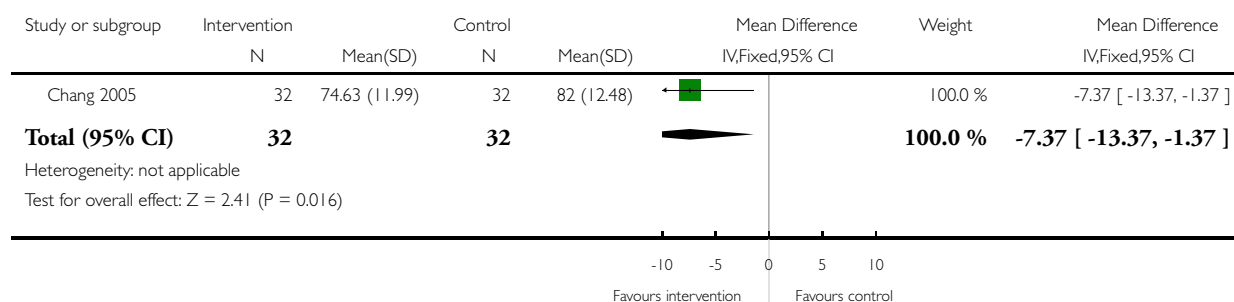


Analysis 1.6. Comparison 1 Music added to standard care (intervention) versus standard care alone (control), Outcome 6 Pulse rate at post-test II.

Review: Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Comparison: 1 Music added to standard care (intervention) versus standard care alone (control)

Outcome: 6 Pulse rate at post-test II

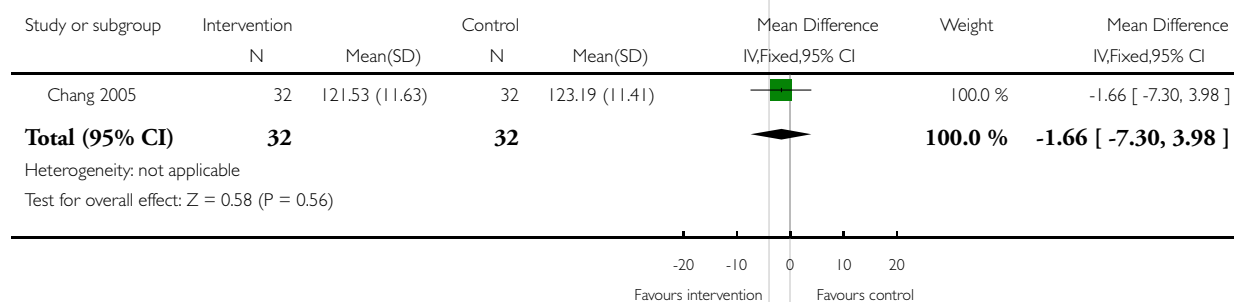


Analysis 1.7. Comparison 1 Music added to standard care (intervention) versus standard care alone (control), Outcome 7 Systolic blood pressure at post-test I.

Review: Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Comparison: 1 Music added to standard care (intervention) versus standard care alone (control)

Outcome: 7 Systolic blood pressure at post-test I

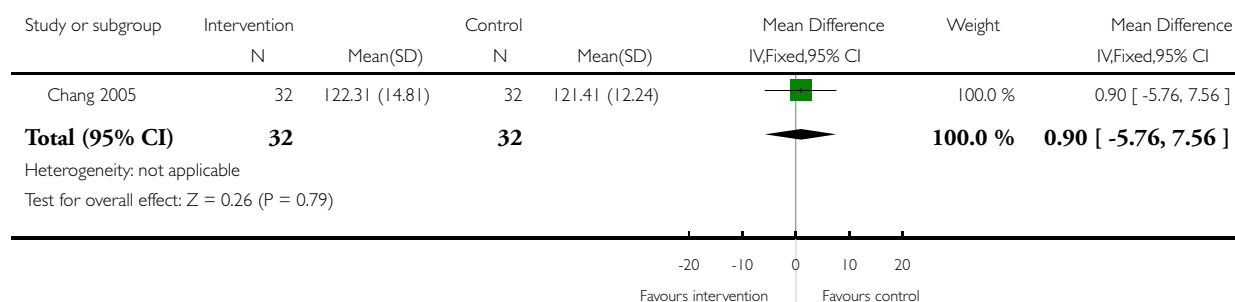


Analysis 1.8. Comparison I Music added to standard care (intervention) versus standard care alone (control), Outcome 8 Systolic blood pressure at post-test-II.

Review: Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Comparison: I Music added to standard care (intervention) versus standard care alone (control)

Outcome: 8 Systolic blood pressure at post-test-II

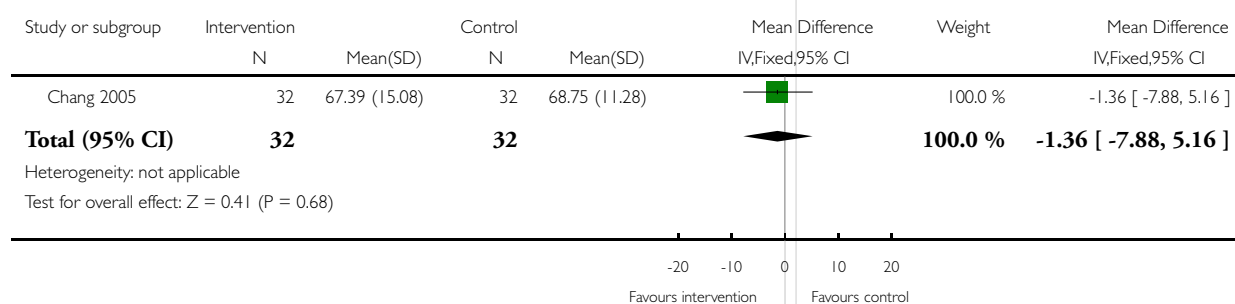


Analysis 1.9. Comparison I Music added to standard care (intervention) versus standard care alone (control), Outcome 9 Diastolic blood pressure at post-test I.

Review: Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Comparison: I Music added to standard care (intervention) versus standard care alone (control)

Outcome: 9 Diastolic blood pressure at post-test I

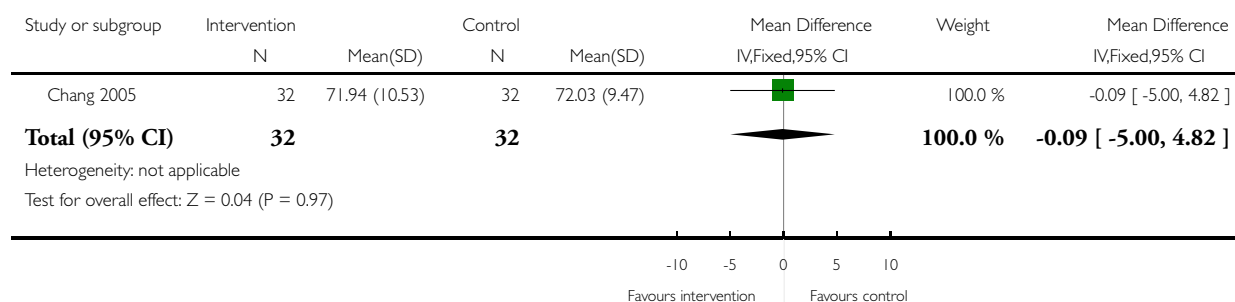


Analysis 1.10. Comparison 1 Music added to standard care (intervention) versus standard care alone (control), Outcome 10 Diastolic blood pressure at post-test II.

Review: Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Comparison: 1 Music added to standard care (intervention) versus standard care alone (control)

Outcome: 10 Diastolic blood pressure at post-test II

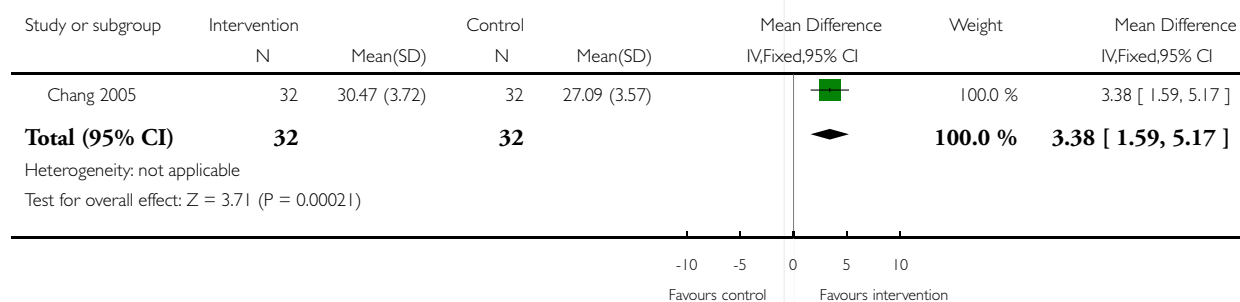


Analysis 1.11. Comparison 1 Music added to standard care (intervention) versus standard care alone (control), Outcome 11 Birth satisfaction at post-test II.

Review: Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Comparison: 1 Music added to standard care (intervention) versus standard care alone (control)

Outcome: 11 Birth satisfaction at post-test II

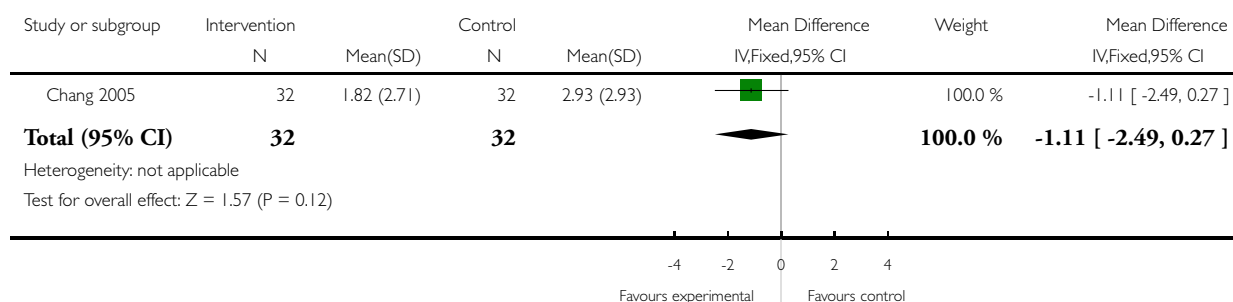


Analysis 1.12. Comparison I Music added to standard care (intervention) versus standard care alone (control), Outcome 12 Anxiety (VASA) score post-test I.

Review: Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Comparison: I Music added to standard care (intervention) versus standard care alone (control)

Outcome: 12 Anxiety (VASA) score post-test I

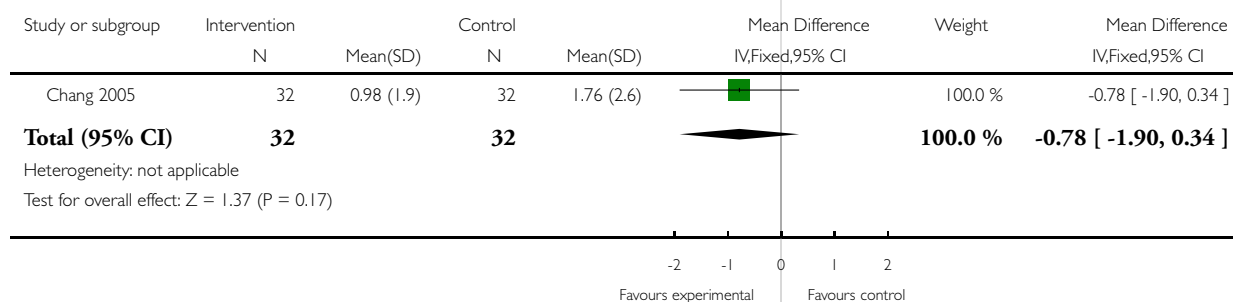


Analysis 1.13. Comparison I Music added to standard care (intervention) versus standard care alone (control), Outcome 13 Anxiety (VASA) score post-test II.

Review: Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Comparison: I Music added to standard care (intervention) versus standard care alone (control)

Outcome: 13 Anxiety (VASA) score post-test II



APPENDICES

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

Data analysis

Measures of treatment effect

In subsequent updates of this review we plan to use standardised mean difference to combine trials measuring the same outcome, but using different methods. For dichotomous data we will use relative risk with 95% confidence intervals (CI) and the corresponding number needed to treat. For continuous data we will use mean differences with 95% confidence intervals (CI) if the outcomes are measured in the same way among trials.

Assessment of heterogeneity

We will assess heterogeneity using the I^2 statistic (Higgins 2003). If we identify high levels of heterogeneity among the trials (exceeding 50%), we will explore it by prespecified subgroup analysis.

Subgroup analyses

We will conduct subgroup analyses classifying for potential sources of heterogeneity including ethnic groups (i.e. Caucasian, African, Latino, and Asian), types of music (i.e. mother's or investigator's preference and genre), methods of music delivery (via loud speakers or headphone), elective versus emergency caesarean section, and primary versus multiple caesarean section, where sufficient data are available. If trials in individual subgroups of the potential factor are thought to be heterogeneous by interaction test as described by Deeks 2001, we will not estimate an overall summary but present each specific subgroup effect size.

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually randomised trials. We will adjust their sample sizes according to the methods described in Gates 2005, using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), or from another source. If ICCs from other sources are used, 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 randomisations unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisations unit and perform a separate meta-analysis. Therefore, the meta-analysis will be performed in two parts as well.

Dealing with missing data

We will analyse data on all participants with available data in the group to which they are allocated, regardless of whether or not they received the allocated intervention. If in the original reports participants are not analysed in the group to which they were randomised, and there is sufficient information in the trial report, we will attempt to restore them to the correct group. In addition, other strategies are planned for handling of missing data. If possible, we will contact the trial authors for requesting missing data. Imputation of missing data following with sensitivity analysis will be performed for considering the impact of missing data on robustness of the results.

Assessment of publication bias

We will consider publication bias using funnel plots of between-treatment effect and its precision on individual trials, and Egger's test (Egger 1997). If we find asymmetrical funnel plots with statistical publication bias, we will further examine the effect of the bias on the meta-analysis conclusion using sensitivity analyses.

Sensitivity analyses

We will carry out sensitivity analyses to explore the effect of trial quality and, where appropriate, cluster-randomised trials, on the review's conclusions. The trial quality will involve an analysis based on concealment of allocation. Trials with clearly inadequate allocation of

concealment will be excluded in order to assess for any substantive difference on the overall result. For the clustering effect, we will perform a sensitivity analysis to see what the effect of different values of the ICC on the results of the analysis would be.

HISTORY

Protocol first published: Issue 1, 2008

Review first published: Issue 2, 2009

14 April 2008	Amended	Converted to new review format.
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CONTRIBUTIONS OF AUTHORS

Malinee Laopaiboon (ML) drafted the protocol and is guarantor for the review. ML, Pisake Lumbiganon (PL), Ruth Martis (RM), Patravoot Vatanasapt (PV) and Bussaba Somjaivong (BS) helped to develop and finalise the protocol. ML, RM and PL selected trial and extracted data. ML did the data analysis. ML and PL drafted the review. RM drafted the plain language summary. ML, PL, RM, PV and BS reviewed drafts and finalised the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Faculty of Public Health, Khon Kaen University, Thailand.
- Faculty of Medicine, Khon Kaen University, Thailand.
- Faculty of Nursing, Khon Kaen University, Thailand.
- Discipline of Obstetrics and Gynaecology, The University of Adelaide, Australia.

External sources

- Thailand Research Fund (Senior Research Scholar), Thailand.
- SEA-ORCHID project, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have updated our methodology for 'Assessment of methodological quality' in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* [Higgins 2008](#).

Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones (Review)

Srisubat A, Potisat S, Lojanapiwat B, Setthawong V, Laopaiboon M



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Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones (Review)

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[Intervention Review]

Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones

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ABSTRACT

Background

Stones in the urinary tract are a common medical problem in the general population. At present, the great expansion in minimally invasive techniques has led to the decrease in open surgery. Extracorporeal shock wave lithotripsy (ESWL) has been introduced as an alternative approach which disintegrates stones in the kidney and upper urinary tract through the use of shock waves. Nevertheless, as there are limitations with the success rate in ESWL, other minimally invasive modalities for kidney stones such as percutaneous nephrolithotomy (PCNL) and retrograde intrarenal surgery (RIRS) are also widely applied.

Objectives

To evaluate the effectiveness and complications of ESWL compared with PCNL or RIRS for managing kidney stones.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL in *The Cochrane Library*), MEDLINE, EMBASE and reference lists of articles without language restriction.

Selection criteria

Randomised controlled trials (RCTs) assessing the use of ESWL compared to PCNL or RIRS for kidney stone management.

Data collection and analysis

Two authors independently assessed all the studies for inclusion. Statistical analyses were performed using the random effects model and the results expressed as risk ratio (RR) for dichotomous outcomes or mean difference (MD) for continuous data with 95% confidence intervals (CI).

Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones (Review)

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Main results

Three studies (214 patients) were included, however results could not be pooled. Two RCTs compared ESWL to PCNL. The success rate at three months for lower pole kidney stones was statistically higher for PCNL (RR 0.39, 95% CI 0.27 to 0.56). Re-treatment (RR 1.81, 95% CI 0.66 to 4.99) and using auxiliary procedures (RR 9.06, 95% CI 1.20 to 68.64) after PCNL were less compared to ESWL. The efficiency quotient (EQ) in PCNL was higher than ESWL. Hospital stay (MD -3.30 days, 95% CI -5.45 to -1.15), duration of treatment (MD -36.00 minutes, 95% CI -54.10 to -17.90) and complications were less for ESWL. One RCT compared ESWL versus RIRS for lower pole kidney stones. The success rate was not significantly different at the end of the third month (RR 0.91, 95% CI 0.64 to 1.30).

Authors' conclusions

Results from three small studies, with low methodological quality, indicated ESWL is less effective for lower pole kidney stones than PCNL but not significantly different from RIRS. Hospital stay and duration of treatment was less with ESWL. More RCTs are required to investigate the effectiveness and complications of ESWL for kidney stones compared to PCNL or RIRS.

PLAIN LANGUAGE SUMMARY

Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones

Stones in the urinary tract are a common medical problem. Fifty per cent of patients with previous urinary stones have a recurrence within 10 years. Kidney stones can cause pain, blood in the urine, infection, decreased kidney function and kidney failure. The treatment is to remove the stones from kidney. Extracorporeal shock wave lithotripsy (ESWL) disintegrates stones using shock waves and is a minimally invasive technique. Other minimally invasive methods (percutaneous nephrolithotomy (PCNL)) and retrograde intrarenal surgery (RIRS)) are widely used for kidney stones management because ESWL had limited success rate. This review aimed to compare the effectiveness and complications between ESWL and stones removing using the nephroscopy through the skin at kidney level (PCNL) or ureteroscope through the bladder and ureter to the kidney (RIRS). Three small randomised studies (214 patients) were included. Two studies compared ESWL with PCNL and one study compared ESWL with RIRS. Patients with lower pole kidney stones who undergo PCNL have a higher success rate than ESWL whereas RIRS was not significantly different from ESWL. However, ESWL patients spent less time in hospital and the duration of treatment was shorter.

BACKGROUND

Urolithiasis (stones in the urinary tract) is a common medical problem with a prevalence of approximately 2% to 3% in the general population. Fifty per cent of patients with previous urinary stones have a recurrence within 10 years (Portis 2001). Additionally, the overall probability of forming kidney stones varies according to age, gender, race, geographic location, climate, occupation. Men are more commonly found to have urinary stones than women (2-3:1), and Caucasians have the highest incidence of upper urinary tract stones compared with Asians, Hispanics and African Americans (Pearle 2007). Kidney stones can also cause serious morbidity, pain, haematuria, infection, decreased kidney function and kidney failure.

At present, the great expansion in minimally invasive techniques has led to the decrease in open surgery. Extracorporeal shock wave lithotripsy (ESWL) has been introduced as an alternative approach and disintegrates stones in the kidney and upper urinary tract through the use of shock waves. However, there are several factors which will affect the choice of treatment for kidney stones including the size, location, and stone composition. For small stones with a maximum diameter of 20 mm or a surface area of 300 mm², ESWL had been established as the standard procedure due to it being non-invasive, having a low rate of complications, and no need for anaesthesia (Tiselius 2006). The overall stone-free rate of ESWL has been reported as 66% (stones 20 mm or less) and 49%

(stones more than 20 mm) (Obek 2001). The stone-free rates at three months for stones are 86% to 89% (renal pelvis), 71% to 83% (upper calyx), 73% to 84% (middle calyx) and 37% to 68% (lower calyx) (Albala 2001; Coz 2000; Maggio 1992; Obek 2001; Turna 2007). Lower caliceal stones have a lower clearance rate after ESWL and the stone size for treatment in this location is generally limited to 10 mm (Albala 2001; Tiselius 2006). The success rate for lower pole stones based on stone size are; 63% to 74% (1-10 mm), 23% to 56% (11-20 mm) and 14% to 33% (21-30 mm) (Albala 2001; Alken 2003). The success rate of ESWL also depends on stone composition. ESWL for uric acid and calcium oxalate dihydrate stones results in a better coefficient of fragmentation than those composed of calcium oxalate monohydrate and cystine. The success rates between these two groups were shown to be 38% to 81% and 60% to 63% respectively (Tiselius 2006).

Currently, the contraindications for ESWL treatment are restricted to pregnancy, severe skeletal malformations, severe obesity, urinary tract obstruction distal to the stone, and aortic and/or renal artery aneurysms. Moreover, ESWL should not be carried out in patients with uncontrolled blood coagulation, uncontrolled hypertension or uncontrolled urinary tract infection (Tiselius 2006). Despite its widespread use for the treatment of stones, ESWL can cause trauma to the kidney. The complications of ESWL are steinstrasse (obstruction due to fragments becoming lodged in the ureter), haematoma, infection, sepsis, hypertension and diabetes mellitus (Krambeck 2006; Riedler 2003).

Due to the limitations of the success rate and the complications of ESWL, other minimal invasive modalities for kidney stones such as percutaneous nephrolithotomy (PCNL) and retrograde intrarenal surgery (RIRS) are widely used. PCNL is indicated for patients with large kidney and upper ureteral stones. The main advantage of PCNL is the higher success rate for these larger stones (May 1998; Netto 1991) as it is not dependent on the stone burden or composition (Tiselius 2006). Pearle 2007 reported that for patients with stones smaller than 10 mm, 100% of patients treated with PCNL were stone-free, compared to 63% for those treated with ESWL. For those patients with stones 11-20 mm, 93% treated with PCNL were stone-free, compared to only 23% of those treated with ESWL. For patients with stones 21-30 mm, 86% treated with PCNL were stone-free, compared to 14% for those treated with ESWL. However, PCNL is more invasive and has a higher associated morbidity than ESWL (Cass 1996; Havel 1998).

With the advance of endourologic technology, RIRS is considered as the second line therapy in the treatment of the ESWL-resistant lower pole stones and for patients with co-morbidities. RIRS management of the kidney stone is a reasonable alternative to ESWL or PCNL in patients with low volume stones (Auge 2001; Chung 2006; Grasso 1999; Holland 2006; Kourambas 2000; Preminger 2006; Stav 2003).

OBJECTIVES

This review aimed to assess the effectiveness and complications of ESWL for kidney stones compared with PCNL or RIRS.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at the outcomes between ESWL and PCNL or RIRS. The first period of randomised cross-over studies were also to be included.

Types of participants

Inclusion criteria

Patients with kidney stones treated using ESWL compared to PCNL or RIRS.

Exclusion criteria

Pregnant women and children with kidney stones were excluded.

Types of interventions

Any patient with kidney stones treated with ESWL compared to PCNL or RIRS.

Types of outcome measures

Primary outcomes

- Success rate: Stone-free, clinically insignificant residual fragments (CIRF) (residual fragment < 4 mm)
- Re-treatment rate
- Auxiliary procedures
- Efficiency quotient (EQ)

Secondary outcomes

- Mean procedural or operating time
- Mean hospital stay
- Complications after treatment

Search methods for identification of studies

Electronic searches

1. The Cochrane Renal Groups specialised register and the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*. CENTRAL and the Renal Groups specialised register contain the handsearched results of conference proceedings from general and speciality meetings. This is an ongoing activity across the Cochrane Collaboration and is both retrospective and prospective ([Master List 2009](#)). Therefore we did not specifically search conference proceedings. Please refer to The Cochrane Renal Review Group's Module in *The Cochrane Library* for the most up-to-date list of conference proceedings ([Renal Group 2009](#)).

2. MEDLINE (from 1966) using the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of RCTs ([Dickersin 1994](#)) with the a specific search strategy developed with input from the Cochrane Renal Groups Trial Search Co-ordinator.

3. EMBASE (from 1980) using a search strategy adapted from that developed for the Cochrane Collaboration for the identification of RCTs ([Lefebvre 1996](#)) with a specific search strategy developed with input from the Cochrane Renal Groups Trial Search Co-ordinator.

See [Appendix 1](#) for search terms used.

Searching other resources

1. Reference lists of nephrology textbooks, review articles and relevant studies.

2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The review was undertaken by five authors (AS, SP, BL, VS, ML). The search strategy described was used to obtain titles and abstracts of studies that were potentially relevant to the review. The titles and abstracts were screened independently by AS, SP and VS, who discarded studies that were not applicable, however studies

and reviews that may have included relevant data or information on studies were retained initially. Authors BL and VS (who are Urologists) independently assessed retrieved abstracts and the full text of these studies to identify studies which satisfied the inclusion criteria.

Data extraction and management

Data extraction was carried out independently by the same authors using standard data extraction forms. Studies reported in non-English language journals were planned to be translated before assessment but we did not find any non-English language articles. Where more than one publication of one study existed, reports were to be grouped together and the most recent or most complete dataset was to be used. Any discrepancy between published versions was to be highlighted. Disagreements were resolved by discussion. Data entry and analysis was performed by ML.

Assessment of risk of bias in included studies

The quality of studies to be included was assessed independently by AS and SP without blinding to authorship or journal using the checklist developed by the Cochrane Renal Group. Discrepancies were resolved by discussion. The items assessed were:

- Sequence generation
- Allocation concealment
- Blinding (patients, investigators, outcome and data assessors)
- Completeness of follow-up
- Selective reporting.

See [Appendix 2](#) for criteria used.

Measures of treatment effect

The mean procedural or operating time and mean hospital stay were assessed using mean difference (MD) with 95% confidence intervals (CI). The risk ratio (RR) with 95% CI was used to assess the success of treatment (stone-free rate, CIRF), re-treatment, and use of auxiliary procedures. The outcomes between studies could not be compared as they used different criteria for measurement. Likewise, due to the difficulty of comparing the complications, we chose to describe the outcomes of each study.

Dealing with missing data

Participants were to be analysed according to the group to which they were randomised, regardless of whether or not they received the allocated intervention, but we could not restore them to the correct group and analyse because information of the missing data in the study reports were not clear.

Assessment of heterogeneity

We could not evaluate the similarity between ESWL and other modalities effect sizes in the included studies because of different study criteria. Therefore, the I^2 statistic ([Higgins 2003](#)) and subgroup analyses were not undertaken.

Assessment of reporting biases

We could not use funnel plots of between-treatment effect and its precision on individual studies for publication bias due to insufficient studies.

Subgroup analysis and investigation of heterogeneity

Initially we planned to conduct subgroup analyses for kidney stone sizes (< 10 mm, 10-20 mm, > 20 mm) and/or stone location (renal pelvis, upper pole, middle pole, and lower pole) and for different comparison interventions of ESWL with PCNL or RIRS but could not because of insufficient data.

Sensitivity analysis

Sensitivity analyses were not conducted to explore the effect of study quality as there were too few studies and different criteria used for measuring outcomes.

RESULTS

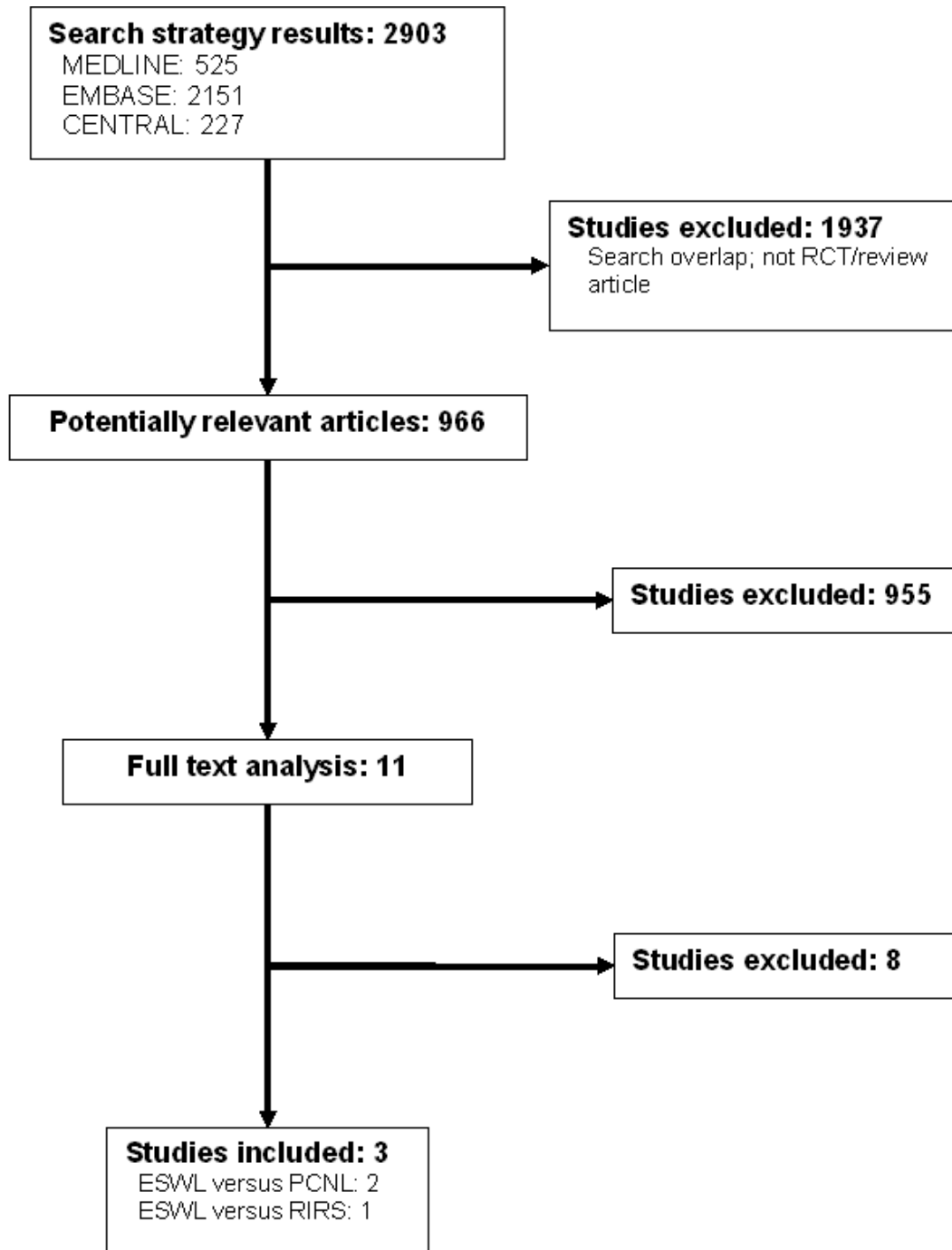
Description of studies

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

Results of the search

The search for studies retrieved 2903 reports and after initial screening we identified 996 potentially relevant titles. Further screening via abstract review identified 11 potentially relevant studies. We retrieved the full-text articles for further evaluation. Eight articles were excluded, six were not RCTs, one was a time series and the other was an editorial comment. Three studies (214 patients) fulfilled our inclusion criteria ([Albala 2001](#); [Carlsson 1992](#); [Pearle 2005](#)). Two were from the USA ([Albala 2001](#); [Pearle 2005](#)) and one from Sweden ([Carlsson 1992](#)). See [Figure 1](#) for study selection procedure.

Figure 1. Flow chart of study selection procedure



Included studies

Two studies compared ESWL and PCNL (Albala 2001; Carlsson 1992) and one compared ESWL and ureteroscopy for lower pole kidney stones (RIRS) (Pearle 2005).

Albala 2001 compared ESWL with PCNL for symptomatic lower pole kidney stones 30 mm or less. This study was supported by a grant from Microvasive. A total of 160 patients aged over 18 were initially randomised however 32 patients were excluded post-randomisation but pre-intervention (withdrew after randomisation (21); stones moved away or passed before surgery (7); violated study protocol (4)). Sixty were enrolled in the ESWL group and 68 in the PCNL group. The mean stone size was 14.43 mm in the ESWL group and 13.59 mm in the PCNL group. Stratified randomisation according to stone sizes of 1-10, 11-20, and 21-30 mm was performed. For ESWL, all lithotriptors were used according to recognised standards. Stone fragments with diameters 3 mm or less were defined as successful ESWL treatment. Most PCNL were performed using a single stage procedure and one centre used a two stage technique. The initial outcome measurements were assessed by the end of the third month. They were stone-free status using nephrotomograms, re-treatment, auxiliary procedures, complications, stone burden, stone composition, quality of life, EQ, and hospital stay.

Carlsson 1992 compared ESWL with PCNL for medium-sized kidney stones (4-30 mm in diameter). Fifty five consecutive patients from one single hospital were randomised, 25 to PCNL (performed at the Karolinska Hospital) and 30 to ESWL (performed at the Linköping University Hospital). There were six exclusions post-randomisation but pre-intervention (PCNL (4), ESWL (2)). Twenty eight patients (mean age 49 years) were treated with ESWL and 21 (mean age 48.2 years) with PCNL. ESWL treatment used an unmodified Dornier HM-3 lithotripter. PCNL was done under epidural anaesthesia with nephrostomy. The outcomes were success rate, hospital stay, duration of treatment, complications and cost/successful treatment. Stone-free or stone fragments 5 mm or less using radiographic examination were considered successful treatment. Follow-up for stone-free rates were reported by the end of the fourth week and at one year.

Pearle 2005 compared ESWL with RIRS using ureteroscopy for lower pole kidney stones 10 mm or less. This study was supported by Boston Scientific, Natick, Massachusetts. Seventy eight patients were randomised in blocks of 10 based on a random number table to undergo ESWL or RIRS. Eleven dropped out before treatment, leaving 67 (ESWL (32), RIRS (35)). The two treatment groups were comparable in age, sex, body mass index, stone size, operative time, hospital stay and complications (intra-and postoperative). Recognised standards for each ESWL machine were used with power settings and number of shock waves used left to the discretion of the individual physician. Ureteroscopes were used for RIRS, including 7.5 Fr and Flex-X™, ACMI Dur 8™ and Dur 8-Elite™ and URF-P3. The use of a ureteral access sheath, intact stone retrieval versus intracorporeal lithotripsy and stent placement were left to the discretion of the individual physician. Stone-free status was determined by plain X-ray by the end of third month or sooner if stone-free. Noncontrast, thin cut computed tomography (5 mm) was required if there was no evidence of residual stones on plain X-ray. Success rate was being stone-free or fragments less than 4 mm.

Risk of bias in included studies

- **Sequence generation:** Two studies described the method of randomisation (Albala 2001; Pearle 2005) and one did not (Carlsson 1992).
- **Allocation concealment:** Information was not provided by any of the included studies.
- **Blinding:** Patients and investigators could not be blinded to the interventions. Blinding of the outcome and data assessors were not described by any of the included studies.
- **Completeness of follow-up:** The analysis was not done under intention-to-treat basis. Patients discontinued their follow-up after treatments in all studies.
- **Selective reporting:** All studies reported the primary outcomes of interest for this review.

See Figure 2, Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Albala 2001	+	?	?	-	+	-
Carlsson 1992	?	?	?	-	+	?
Pearle 2005	+	?	?	-	+	-

Effects of interventions

Success of treatment

Treatment success was defined as stone-free or clinically insignificant residual fragments (CIRF) (residual fragment < 4 mm).

We were unable to combine the stone-free rates between two studies because they were not measured for the same time period or size of fragment stones. [Albala 2001](#) reported the overall stone-free status (stone fragments ≤ 3 mm in diameter) and according to initial stone size at the end of the third month. [Carlsson 1992](#) measured the stone-free status (free of stones or fragments ≤ 5 mm) at the end of the fourth week and at one year.

[Albala 2001](#) reported success rates of 37% for ESWL and 95% for PCNL. The difference in success between the two interventions was significant ([Analysis 1.1.2](#): RR 0.39, 95% CI 0.27 to 0.56). According to stone size (1-10, 11-20 and 21-30 mm), the success

was 63% (12/19), 23% (6/26) and 14% (1/7) for ESWL and 100% (20/20), 93% (26/28) and 86% (6/7) for PCNL. There was a significant increase in success with PCNL for stone sizes 1-10 mm ([Analysis 1.1.4](#): RR 0.64, 95% CI 0.45 to 0.90) and 11-20 mm ([Analysis 1.1.5](#): RR 0.25, 95% CI 0.12 to 0.51) but not for 21-30 mm stones ([Analysis 1.1.6](#): RR 0.17, 95% CI 0.03 to 1.05), however the numbers in each group were small.

[Carlsson 1992](#) reported success rates of 76% (19/25) for ESWL and 100% (15/15) for PCNL at the end of the fourth week ([Analysis 1.1.1](#): RR 0.77, 95% CI 0.61 to 0.98). At one year these were 77% (20/26) for ESWL and 94% (18/19) for PCNL ([Analysis 1.1.3](#): RR 0.81, 95% CI 0.64 to 1.03).

[Pearle 2005](#) reported stone-free rates of 65% (17/26) for ESWL and 72% (23/32) for RIRS at the end of the third month. The difference was not significant ([Analysis 2.1](#): RR 0.91, 95% CI 0.64 to 1.30).

Re-treatment

Re-treatment was necessary for 10/64 (16%) in the ESWL group and 5/58 (9%) in the PCNL group (Albala 2001). This difference was not significant (Analysis 1.2.1: RR 1.81, 95% CI 0.66 to 4.99). Re-treatment according to stone size (1-10, 11-20 and 21-30 mm) was 9%, 18% and 22% for ESWL and 10%, 3% and 25% for PCNL respectively. The differences were not significant for any of the stone size categories (Analysis 1.2.2 (1-10 mm): RR 0.91, 95% CI 0.14 to 5.86; Analysis 1.2.3 (11-20 mm): RR 5.27, 95% CI 0.67 to 41.26; Analysis 1.2.4 (21-30 mm): RR 1.00, 95% CI 0.18 to 5.63). Carlsson 1992 did not report re-treatment data. Pearle 2005 reported secondary treatments were necessary for five ESWL patients and two RIRS patients (see Characteristics of included studies).

Auxiliary procedures

There were 10/64 (16%) auxiliary procedures in the ESWL group and 1/58 (2%) in the PCNL group (Albala 2001) and this was statistically significant (Analysis 1.3.1: RR 9.06, 95% CI 1.20 to 68.64). Auxiliary procedures according to stone sizes (1-10, 11-20 and 21-30 mm) were 14% (3/22), 21% (7/33) and 0% for ESWL respectively and were only performed in 1/29 (3%) patients in the 11-20 mm PCNL group. The differences were not significant (Analysis 1.3.2 (1-10 mm): RR 6.39, 95% CI 0.35 to 116.57; Analysis 1.3.3 (11-20 mm): RR 6.15 (95% CI 0.80 to 47.07). Carlsson 1992 did not report auxiliary procedures.

Efficiency quotient (EQ)

We calculated overall EQ for Albala 2001 which was 28% for ESWL and 86% for PCNL. However, EQ decreased when stone size increased. It accounted for 51%, 17% and 12% in the ESWL group and 91%, 88% and 71% in the PCNL group for stone sizes 1-10, 11-20 and 21-30 mm respectively. There was no EQ shown in the studies of Carlsson 1992 or Pearle 2005.

Mean procedural and operating times

Procedural time was not reported in Albala 2001. In Carlsson 1992, the duration of treatment was 43 ± 13.8 minutes for ESWL and 79 ± 40.6 minutes for PCNL. The mean duration of treatment was significantly longer for PCNL (Analysis 1.4: MD -36.0 min, 95% CI -54.1 to -17.9).

The mean operating time in Pearle 2005 was 65.5 ± 27.9 minutes for ESWL and 90.4 ± 43.8 minutes for RIRS. The mean operating time was significantly longer for RIRS (Analysis 2.2: MD -24.9 min, 95% CI -42.34 to -7.46).

Mean hospital stay

Albala 2001 reported a mean hospital stay of 0.55 days (range 0-9) for ESWL and 2.66 days (range 1-7) for PCNL. We could not

determine the MD between the two interventions because SDs were not reported.

Carlsson 1992 reported a mean hospital stay of 4.1 days (± 2.6) for ESWL and 7.4 days (± 4.5) for PCNL. The mean hospital stay was significantly shorter for ESWL (Analysis 1.5: MD -3.3 days, 95% CI -5.45 to -1.15).

In the study of Pearle 2005, all patients were discharged home on the day of treatment in the ESWL group, whereas 94% of patients had to stay 0.06 days in hospital after RIRS. We could not determine the MD between the two interventions because the SDs were not reported.

Complications after treatment

Albala 2001 reported the complications for ESWL were; urinary tract infection (1), obstruction (2), colic (2), haematoma (1) and steinstrasse (1). For PCNL the reported complications were; urinary tract infection (1), ileus (3), sepsis (1), haematoma (2), obstruction (1), perforation (3), transfusion (1) and arteriovenous fistula (1).

The complications in Carlsson 1992 were haematuria and fever (over 38°C). Pain was not considered a complication. They measured complications at days 1, 3, 5, 7, and 9. The period of haematuria in ESWL group was longer than in the PCNL group. Haematuria was still present at day 9 in the ESWL group but not in the PCNL group. Fever was reported less in the ESWL group than the PCNL group.

Pearle 2005 reported intra- and postoperative complications. There were 1/32 (3%) Intraoperative complications in the ESWL group and 7/35 (20%) in the RIRS group. There were 7/30 (23%) postoperative complications in the ESWL group and 7/33 (21%) in RIRS group.

DISCUSSION

Summary of main results

This review showed that for treating lower pole kidney stones, PCNL had a significantly higher success rate in terms of being stone-free than ESWL. Treatment success did not differ significantly between RIRS and ESWL. The use of auxiliary procedures were higher in ESWL, however ESWL required less time in hospital and had shorter procedural times.

Overall completeness and applicability of evidence

Two RCTs fulfilled our inclusion criteria and presented the clinical effects between ESWL and PCNL (Albala 2001; Carlsson 1992)

and one study compared ESWL and RIRS for lower pole kidney stones (Pearle 2005). The study by Carlsson 1992 was performed in the early period of ESWL technology and the success criteria for treating kidney stones was measured differently to the later study by Albala 2001. Albala 2001 focused on lower pole kidney stones while Carlsson 1992 did not specify stone location, thus we could not combine the data. The present technology for ESWL reduces the time required to stay in hospital. As a result, the information on hospital stay for ESWL compared to PCNL and RIRS seems less relevant.

Quality of the evidence

None of the included studies provided any information about allocation concealment. Patients and investigators could not be blinded and there were no information about blinding of either the outcome or data assessors in these studies. There were missing patients during the follow-up of all studies but the reasons were not reported. Thus, intention-to-treat was not used to analyse the outcome results. Two studies were supported by the medical device companies (Albala 2001; Pearle 2005). These factors limited the methodological strength of the evidence.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to support the use of ESWL for removing stones from the kidney. This review has shown that for treating lower pole kidney stones, PCNL had a significantly higher success rate in terms of stone-free kidneys than ESWL. The success of RIRS did not differ significantly from ESWL. However, the use of ESWL resulted in less time in hospital and shorter treatment duration when compared to PCNL or RIRS.

Implications for research

Larger RCTs with good methodology comparing ESWL and PCNL or RIRS for kidney stone management are required to evaluate effectiveness and complications, and to determine which modality is more effective for kidney stones. Studies should have standardised outcome measurements including data on quality of life and health economics.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Albala 2001

Methods	- Country: USA - Setting: multicentre (18 institutions) - Design: Parallel RCT - Time frame: 3 months (initial results) - Intention-to-treat: Not performed - Follow-up period: 3 months after treatment - Loss to follow-up (at 3 months after treatment): 16.4% (21/128)
Participants	Inclusion criteria: - Patients older than 18 years - Stone burden ≤ 30 mm in aggregate diameter - Lower pole stones only - Patients agreeable to randomisation between shock wave lithotripsy and percutaneous stone removal ESWL group - Number: 68 - Age: NS - Sex(M/F): NS - Mean stone size: 13.59 mm PCNL group - Number: 60 - Age: NS - Sex(M/F): NS - Mean stone size: 14.43 mm Exclusion criteria - Ureteropelvic junction obstruction - Caliceal diverticulum - Infundibular stenosis - Shock wave lithotripsy or percutaneous stone removal complicated or not feasible due to body size or habitus, coagulopathy - Stones in renal pelvis, ureter, or mid or upper pole calices - Renal insufficiency with SCr > 3.0 mg/dL - Cystinuria - Kidney transplant - Patients undergoing simultaneous bilateral stone procedures - Pregnancy
Interventions	ESWL - Lithotriptors represented and used according to recognized standards - Modified and unmodified Dornier HM3 (Dornier Medical Systems) - Dornier MFL 5000 (Dornier Medical Systems) - Lithostar (Siemens Medical Systems) - Lithostar Shock Tube C (Siemens Medical Systems) - Medstone STS (Medstone International Inc., Aliso Viejo, California)

	○ Direx Tripter Compact (Direx) ○ Dornier HM4 (Dornier Medical Systems) ○ Storz Modulith (Storz Medical, Kreuzlingen, Switzerland) 2. Treatment goal of ESWL was to achieve fragments ≤ 3 mm in diameter 3. Ureteral stenting for stones between 15 and 25 mm was left to the discretion of the investigator. PCNL ● Most PCNL performed a single stage procedure in the operation ● One centre used 2 stage procedure	
Outcomes	Primary 1. Stone-free rate (for ESWL was stone fragments ≤ 3 mm) ○ Overall ○ According to stone size (1-10, 11-20 and 21-30 mm) 2. Re-treatment rate 3. Auxiliary procedure 4. EQ Secondary 1. Hospital stay 2. Complications 3. Stone burden 4. Stone composition 5. Quality of life	
Notes	Funding: Supported by a grant from Microvasive Exclusion post randomisation but pre-intervention ● Withdrew after randomisation (21) ● Stone moved or passed before surgery (7) ● Violated protocol (4) Completeness of follow-up ● Patients randomised: 160 ● Enrolled: 128 (ESWL (68), PCNL (60)) ● Analysed: 107 (ESWL (52), PCNL (55)) ● Follow-up at 3 months: 88% (107/121)	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomised schedule for each site and stratified by stone size (1-10, 11-20 and 21-30 mm)
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Not feasible to be blinded to participants or investigators. No blinding information of outcomes assessors or data assessors

Albala 2001 (Continued)

Incomplete outcome data addressed? All outcomes	No	There were patients lost to follow-up after interventions
Free of selective reporting?	Yes	The expected outcomes were reported according to the objectives
Free of other bias?	No	Funding: Supported by a grant from Microvasive

Carlsson 1992

Methods	- Country: Sweden - Setting: Karolinska Hospital and Linköping University Hospital - Design: Parallel - Time frame: 1 year - Intention-to-treat: Not performed - Follow-up period: 4 months and 1 year after treatment - Loss to follow-up 9 patients at 4 weeks: ESWL (3), PCNL (6) 4 patients at one year: ESWL (2), PCNL (2)
Participants	Inclusion criteria - Patients with stones of 4-30 mm in diameter - Patients eligible for either ESWL or PCNL ESWL group - Number: 28 - Age: 49.0 years - Sex (M/F): 20/8 - Mean number of stones/patient: 3.4 - Mean size of largest stone: 13 mm (range 5-27 mm) PCNL group - Number: 21 - Age: 48.2 years - Sex(M/F): 12/9 - Mean number of stones/patient: 2.8 - Mean size of largest stone: 12 mm (range 7-25 mm) Exclusions: NS
Interventions	ESWL - Unmodified Dornier HM-3 lithotripter PCNL - Done under epidural anaesthesia in the department of diagnostic radiology with the collaboration of a radiologist and a urologist - Nephrostomy was made with the patient in prone, and the track was dilated to 27 French scale. - Nephroscope was introduced and the stone was usually extracted with forceps under fluoroscopic control. - Ultrasonic disintegration was used for stones > 15 mm.

	Nelaton catheter 20 French scale was used for nephrostomy, often with a coaxial pigtail catheter to keep it in place.	
Outcomes	Primary - Success rate (stone-free or fragments ≤ 5 mm) - Four weeks - One year Secondary - Hospital stay - Duration of treatment - Complications	
Notes	Funding: NS Exclusion post randomisation but pre-intervention - ESWL group: 2 were excluded (pregnancy (1), malignant disease (1)) - PCNL group: 4 did not have operation (passed their stones naturally (2), moved to another area (1), preferred to have ESWL (1)) Completeness of follow-up 55 consecutive patients from one single hospital, the Karolinska Hospital, Stockholm, met the inclusion criteria (25 were randomised to have PCNL at the Karolinska Hospital and 30 have ESWL at Linköping University Hospital) - Patients treated: 49 (ESWL (28), PCNL (21)) - Stone-free status 4 weeks: ESWL (25), PCNL (15) 1 year: ESWL (26), PCNL (19) - Follow-up at 4 weeks and 1 year were 81.6% (40/49) and 91.8% (45/49) respectively	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No information of sequence generation
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Not feasible to blind participants or investigators. Blinding of outcomes assessors and data assessors not stated
Incomplete outcome data addressed? All outcomes	No	There were patients lost of follow-up after interventions
Free of selective reporting?	Yes	The expected outcomes were reported according to the objectiveness.
Free of other bias?	Unclear	No information on funding

Methods	- Country: USA - Setting: multi-centre (19 institutions) - Design: Parallel - Time frame: NS - Intention-to-treat: Not performed - Follow-up period - Initial follow-up: 2-6 weeks after treatment documented re-treatments, secondary procedures and complications - Stone-free status: 3 months after treatment - Loss to follow-up: 13.4% (9/67) at 3 months
Participants	Inclusion criteria - Adult patients with isolated, ≤ 1 cm lower pole stones ESWL group - Number: 32 - Mean age $\pm$ SD: 52.5 ± 12.3 years - Sex(M/F): 19/13 - Body mass index $\pm$ SD: 26.9 ± 8.1 - No. rt/lr stones: 11/21 - Mean stone surface area $\pm$ SD: 42.2 ± 21.2 mm² RIRS group - Number: 35 - Mean age $\pm$ SD: 49.3 ± 14.2 years - Sex(M/F): 17/18 - Body mass index $\pm$ SD: 28.1 ± 6.6 - No. rt/lr stones: 14/21 - Mean stone surface area $\pm$ SD: 35.9 ± 18.4 mm² Exclusions criteria - Same size non lower pole stones - Ureteral stricture or ureteropelvic junction obstruction - Infundibular stenosis or caliceal diverticulum associated with target stone - A transplant, pelvic or solitary kidney - Kidney insufficiency (SCr > 3.0 mg/dL) - Pregnancy - Previous failed treatment - Cystinuria - Urinary diversion - Impassable urethral stricture - Planned simultaneous treatment of contralateral stones - Active urinary tract infection or an immunocompromised state
Interventions	ESWL - Lithotriptors used in study with recognized standards for each machine - Doli-S (Dornier Medtech, Kennesaw, Georgia) - HM3 (Dornier) - MFL-5000 (Dornier) - LithoTron - Lithostar - Lithostar Plus - Modulith

	○ Econolith ○ Medstone STS 2. Power settings and number of shock wave administered were left to the discretion of the treating physician with the intent of achieving a fragment size ≤ 3 mm. RIRS 1. A variety of ureteroscopes were used, including ○ 7.5 Fr and Flex-X™ (Karl Storz Endoscopy-America, Culver, California) ○ ACMI Dur 8™ and Dur 8-Elite™ (ACMI, Southborough, Massachusetts) ○ URF-P3 (Olympus, Melville, New York) 2. Dilatation of the intramural ureter was performed as needed. 3. Use of a ureteral access sheath, intact stone retrieval versus intracorporeal lithotripsy and stent placement were left to investigator discretion	
Outcomes	Primary 1. Success rate (stone-free or fragments < 4 mm) Secondary 1. Re-treatment 2. Hospital stay (days) 3. Operating time (min) 4. Complications ○ Intraoperative complications ○ Postoperative complications	
Notes	Exclusion post randomisation but pre-intervention ● Dropped out of the study before treatment: 11 Completeness of follow-up ● Patients randomised: 78 ● Treated on protocol: 67 (ESWL (32), URS (35)) ● Analysed at the end of 3rd month: 58 (ESWL (26), URS (32)) ● Follow-up at the end of 3rd month: 86.6% (58/67) Outcomes ● Re-treatment ○ 5 ESWL patients: ESWL in 2, RIRS in 1 for target stone treatment and RIRS in 2 for obstructing ureteral fragments ○ 2 URS patients: RIRS in 1 for target stone treatment and 1 underwent RIRS for an obstructing fragment	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Using blocks of 10 according to a random number table
Allocation concealment?	Unclear	No stated
Blinding? All outcomes	Unclear	Not feasible to blind participants or investigators. Blinding of outcomes assessors and data assessors not stated

Pearle 2005 (Continued)

Incomplete outcome data addressed? All outcomes	No	There were patients lost of follow-up after interventions.
Free of selective reporting?	Yes	The expected outcomes were reported according to the objectiveness.
Free of other bias?	No	Funding: Supported by Boston Scientific

EQ - efficiency quotient; ESWL - extracorporeal shock wave lithotripsy; NS - not stated; PCNL - percutaneous nephrolithotomy; RIRS - retrograde intrarenal surgery; SCr - serum creatinine

Characteristics of excluded studies [ordered by study ID]

Carr 1996	Not RCT or quasi-RCT for the allocation of the treatments between ESWL and PCNL.
Charig 1986	Time-series treatments among open surgery, PCNL, and ESWL.
Eterovic 2005	Not RCT or quasi-RCT for the allocation of the treatments between ESWL and PCNL.
Liou 2001	Not RCT or quasi-RCT for the allocation of the treatments between ESWL and PCNL.
Mays 1988	Not RCT or quasi-RCT for the allocation of the treatments between ESWL and PCNL.
Menon 1993	Editorial comment.
Turna 2007	Not RCT or quasi-RCT for the allocation of the treatments between ESWL and PCNL.
You 2006	Not RCT or quasi-RCT for the allocation of the treatments between ESWL and PCNL.

DATA AND ANALYSES

Comparison 1. ESWL versus PCNL

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Success of treatment	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Success at 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.2 Success at 3 months	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.3 Success at 1 year	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.4 Success at 3 months according to stone size (1-10 mm)	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.5 Success at 3 months according to stone size 11-20 mm)	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.6 Success at 3 months according to stone size 21-30 mm)	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2 Re-treatment	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Overall re-treatment	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.2 Re-treatment according to stone size (1-10 mm)	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.3 Re-treatment according to stone size (11-20 mm)	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.4 Re-treatment according to stone size (21-30 mm)	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
3 Auxiliary procedures	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Overall auxiliary procedures	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.2 Auxiliary procedures according to stone size (1-10 mm)	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.3 Auxiliary procedures according to stone size (11-20 mm)	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.4 Auxiliary procedures according to stone size (21-30 mm)	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
4 Procedural and operating time (minutes)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Hospital stay (days)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Comparison 2. ESWL versus RIRS

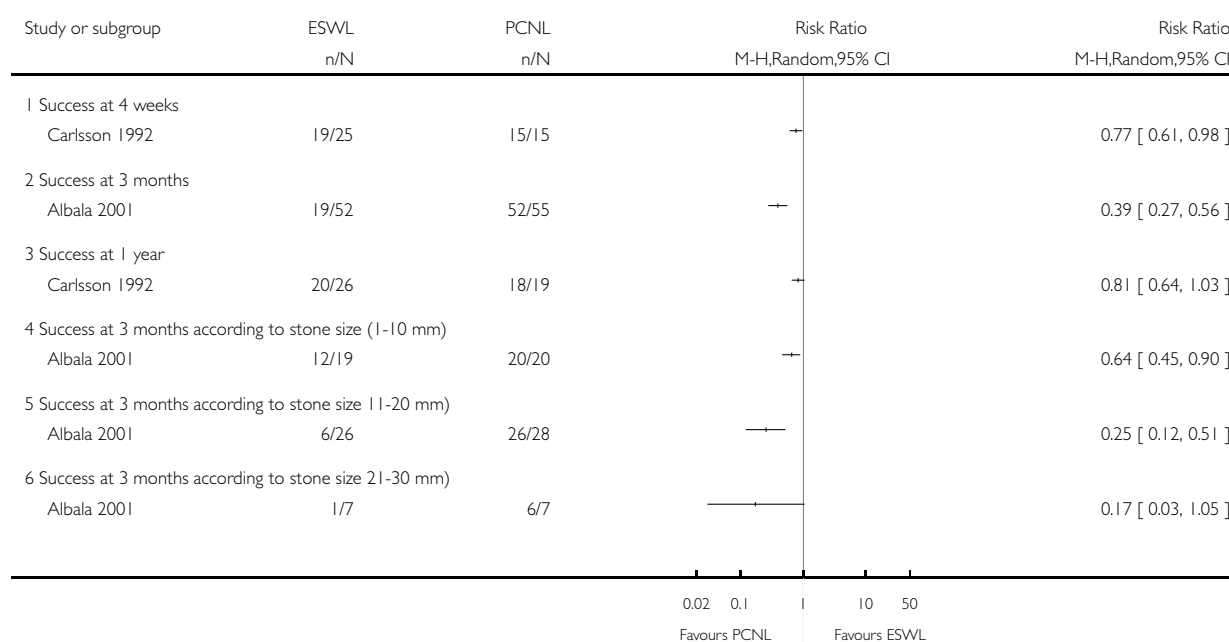
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Success of treatment	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Success at 3 months	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2 Procedural and operating time (minutes)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 ESWL versus PCNL, Outcome 1 Success of treatment.

Review: Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones

Comparison: 1 ESWL versus PCNL

Outcome: 1 Success of treatment

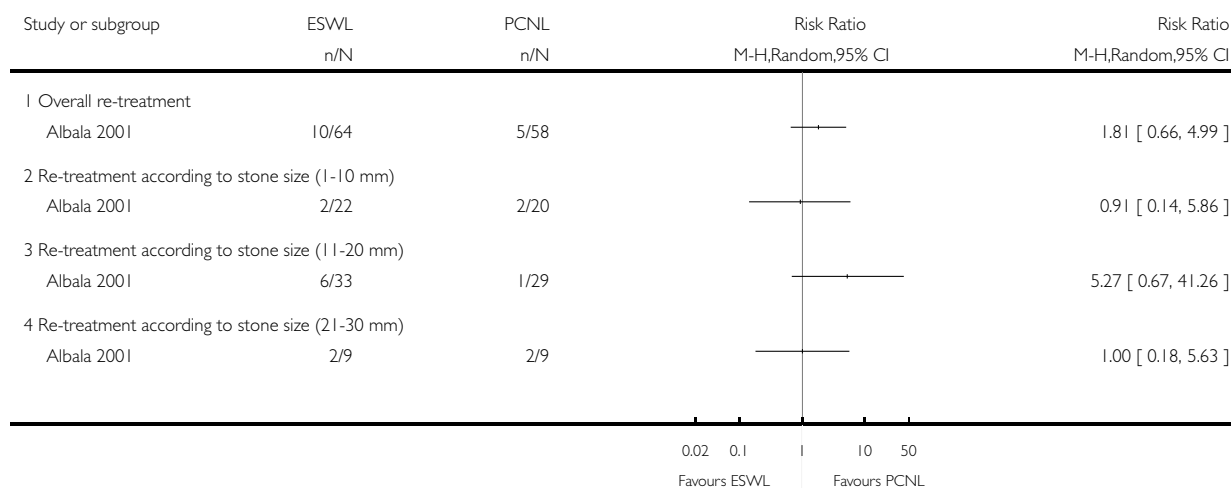


Analysis 1.2. Comparison 1 ESWL versus PCNL, Outcome 2 Re-treatment.

Review: Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones

Comparison: 1 ESWL versus PCNL

Outcome: 2 Re-treatment

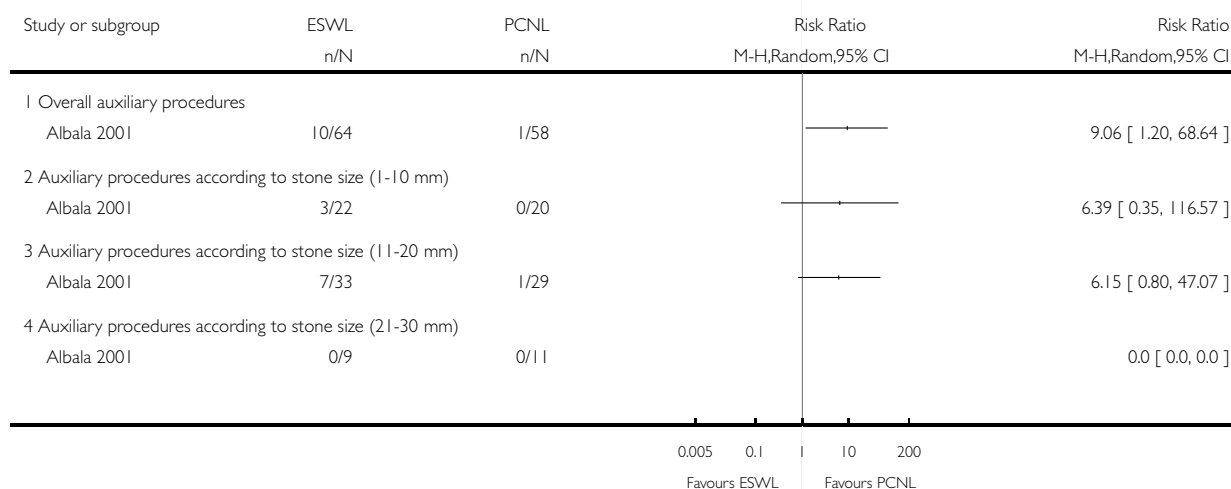


Analysis 1.3. Comparison 1 ESWL versus PCNL, Outcome 3 Auxiliary procedures.

Review: Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones

Comparison: 1 ESWL versus PCNL

Outcome: 3 Auxiliary procedures

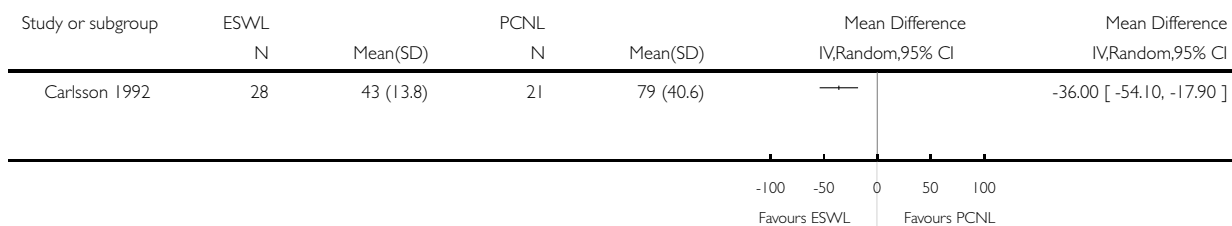


Analysis 1.4. Comparison 1 ESWL versus PCNL, Outcome 4 Procedural and operating time (minutes).

Review: Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones

Comparison: 1 ESWL versus PCNL

Outcome: 4 Procedural and operating time (minutes)

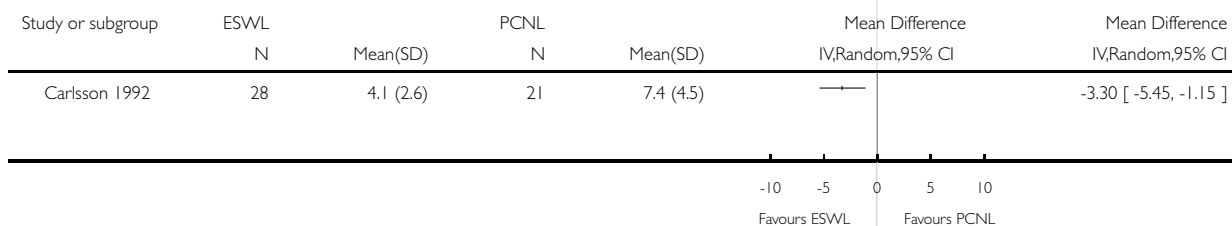


Analysis 1.5. Comparison 1 ESWL versus PCNL, Outcome 5 Hospital stay (days).

Review: Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones

Comparison: 1 ESWL versus PCNL

Outcome: 5 Hospital stay (days)

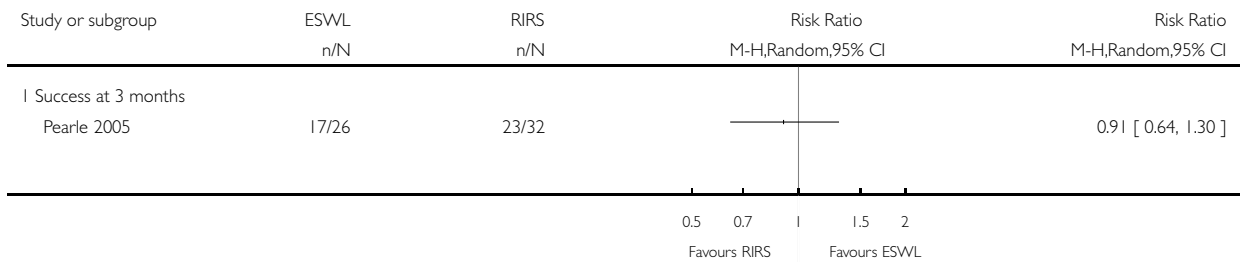


Analysis 2.1. Comparison 2 ESWL versus RIRS, Outcome 1 Success of treatment.

Review: Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones

Comparison: 2 ESWL versus RIRS

Outcome: 1 Success of treatment

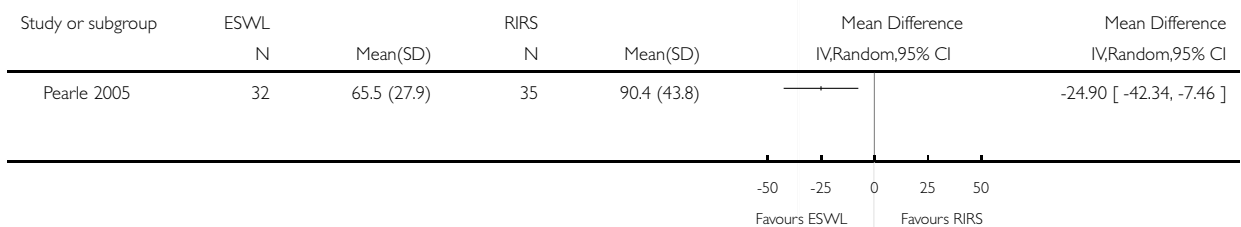


Analysis 2.2. Comparison 2 ESWL versus RIRS, Outcome 2 Procedural and operating time (minutes).

Review: Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones

Comparison: 2 ESWL versus RIRS

Outcome: 2 Procedural and operating time (minutes)



APPENDICES

Appendix I. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor Lithotripsy, this term only 2. (eswl or swl):ti,ab,kw in Clinical Trials 3. shockwave lithotrip*:ti,ab,kw in Clinical Trials 4. extracorporeal shockwave lithotrip*:ti,ab,kw in Clinical Trials 5. electrohydraulic shockwave lithotrip*:ti,ab,kw in Clinical Trials 6. ultrasonic lithotrip*:ti,ab,kw in Clinical Trials 7. (retrograde intrarenal surgery):ti,ab,kw in Clinical Trials 8. rirs:ti,ab,kw in Clinical Trials 9. MeSH descriptor Nephrostomy, Percutaneous, this term only 10. pcnl:ti,ab,kw in Clinical Trials 11. percutaneous nephrolithotom*:ti,ab,kw in Clinical Trials 12. percutaneous nephrolithotrip*:ti,ab,kw in Clinical Trials 13. flexible ureteroscop*:ti,ab,kw in Clinical Trials 14. endorenal surgery:ti,ab,kw in Clinical Trials 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 Urolithiasis explode all trees 17. (kidney* AND (stone* OR calcul*)):ti,ab,kw in Clinical Trials 18. (urin* AND (stone* OR calcul*)):ti,ab,kw in Clinical Trials 19. nephrolithiasis:ti,ab,kw in Clinical Trials 20. (#16 OR #17 OR #18 OR #19) 21. (#15 AND #20)
MEDLINE	1. Lithotripsy/ 2. (eswl or swl).tw. 3. shockwave lithotrip\$.tw. 4. extracorporeal shockwave lithotrip\$.tw. 5. electrohydraulic shockwave lithotrip\$.tw. 6. ultrasonic lithotrip\$.tw. 7. Nephrostomy, Percutaneous/ 8. percutaneous nephrolithotom\$.tw. 9. percutaneous nephrolithotrip\$.tw. 10. endorenal surgery.tw. 11. pcnl.tw. 12. retrograde intrarenal surgery.tw. 13. flexible ureteroscop\$.tw. 14. rirs.tw. 15. or/1-14 16. exp Urolithiasis/ 17. urinary lithiasis.tw. 18. (kidney\$ and (stone\$ or calcul\$)).tw. 19. (urin\$ and (stone\$ or calcul\$)).tw. 20. nephrolithiasis.tw. 21. or/16-20

(Continued)

	22. and/16,21
EMBASE	1. LITHOTRIPSY/ 2. extracorporeal lithotripsy/ 3. ultrasonic lithotripsy/ 4. (eswl or swl).tw. 5. extracorporeal shockwave lithotrip\$.tw. 6. electrohydraulic shockwave lithotrip\$.tw. 7. ultrasonic lithotrip\$.tw. 8. Percutaneous Nephrolithotomy/ 9. percutaneous nephrolithotom\$.tw. 10. percutaneous nephrolithotrip\$.tw. 11. pcnl.tw. 12. retrograde intrarenal surgery.tw. 13. rirs.tw. 14. flexible ureteroscopy\$.tw. 15. endorenal surgery.tw. 16. or/1-15 17. exp Urolithiasis/ 18. urolithiasis.tw. 19. urinary lithiasis.tw. 20. ureterolithiasis.tw. 21. (kidney\$ and (stone\$ or calcul\$)).tw. 22. (urin\$ and (stone\$ or calcul\$)).tw. 23. nephrolithiasis.tw. 24. or/17-23 25. and/16,24

Appendix 2. Quality assessment checklist

Sequence generation

- Yes: Randomisation method presented such as random number table, computer random number generator.
- Unclear: Randomisation stated but no information on method used was available.
- No: Method of randomisation used such as date of birth, day of visit, ID or record number, alternate allocation.

Allocation concealment

- Yes: Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study.
- Unclear: Randomisation stated but no information that investigator/participant could not influence intervention group.
- No: Method of randomisation used such as alternate medical record numbers or unsealed envelopes; any information in the study that indicated that investigators or participants could influence intervention group.

Blinding

- Blinding of outcome assessor: Yes/unclear/no.
- Blinding of data analysis: Yes/unclear/no.

Completeness of follow-up

- Per cent of participants excluded or lost to follow-up.

Selective reporting

- Free of selective reporting: Yes/unclear/No

HISTORY

Protocol first published: Issue 2, 2008

Review first published: Issue 4, 2009

CONTRIBUTIONS OF AUTHORS

- Writing of protocol and review: AS, SP, BL, VS, ML
- Screening of titles and abstracts: AS, SP, VS
- Assessment for inclusion: BL, VS
- Risk of bias assessment: AS, SP
- Data extraction: AS, SP
- Data entry into RevMan: ML
- Data analysis: ML

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Department of Medical Services, Ministry of Public Health, Thailand.
- Faculty of Medicine, Chiangmai University, Thailand.
- Department of Surgery, Lerdsin Hospital, Thailand.
- Faculty of Public Health, Khon Kaen University, Thailand.

External sources

- Thailand Research Fund (Senior Research Scholar), Thailand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

With the introduction of RevMan 5 and the new risk of bias assessment criteria, the quality items that we assessed were different from those stated in the protocol. Sequence generation, allocation concealment, blinding, completeness of follow-up and selective reporting were used to assess study quality.

INDEX TERMS

Medical Subject Headings (MeSH)

*Lithotripsy; *Nephrostomy, Percutaneous; Kidney Calculi [surgery; *therapy]; Randomized Controlled Trials as Topic; Ureteroscopy

MeSH check words

Humans

Epidural blood patching for preventing and treating post-dural puncture headache (Review)

Boonmak P, Boonmak S



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[Intervention Review]

Epidural blood patching for preventing and treating post-dural puncture headache

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ABSTRACT

Background

This is an update of a Cochrane Review first published in Issue 2, 2002. Dural puncture is a common procedure, but leakage of cerebrospinal fluid (CSF) from the resulting dural defect may cause post-dural puncture headache (PDPH) after the procedure, and this can be disabling. Injecting an epidural blood patch around the site of the defect may stop this leakage.

Objectives

To assess the possible benefits and harms of epidural blood patching in both prevention and treatment of PDPH.

Search strategy

We searched the Cochrane PaPaS Group Trials Register; CENTRAL; MEDLINE and EMBASE in April 2009.

Selection criteria

We sought all randomised controlled trials (RCTs) that compared epidural blood patch versus no epidural blood patch in the prevention or treatment of PDPH among all types of participants undergoing dural puncture for any reason. The primary outcome of effectiveness was postural headache.

Data collection and analysis

One review author extracted details of trial methodology and outcome data from studies considered eligible for inclusion. We invited authors of all such studies to provide any details that were unavailable in the published reports. We performed intention-to-treat (ITT) analyses using the Peto O-E method. We also extracted information about adverse effects (post-dural puncture backache and epidural infection).

Main results

Nine studies (379 participants) were eligible for inclusion. Prophylactic epidural blood patch improved PDPH compared to no treatment (OR 0.11, 95% CI 0.02 to 0.64, one study), conservative treatment (OR 0.06, 95% CI 0.03 to 0.14, two studies) and epidural saline patch (OR 0.16, 95% CI 0.04 to 0.55, one study). However, prophylactic epidural blood patch did not result in less PDPH than a sham procedure (one study). Therapeutic epidural blood patch resulted in less PDPH than conservative treatment (OR 0.18, 95% CI 0.04 to 0.76, one study) and a sham procedure (OR 0.04, 95% CI 0.00 to 0.39, one study). Backache was more common with epidural blood patch. However, these studies had very small numbers of participants and outcome events, as well as uncertainties about trial methodology, which preclude reliable assessments of the potential benefits and harms of the intervention.