รายงานวิจัยฉบับสมบูรณ์

โครงการสนับสนุนการวิจัยทางระบาดวิทยาคลินิกและการวิจัยเชิงสังเคราะห์

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สนับสนุนโดยสำนักงานกองทุนสนับสนุนการวิจัย

บทคัดย่อ

ความรู้ทางด้านระบาดวิทยาคลินิกจะช่วยให้นักวิจัยสร้างโครงการวิจัยที่เหมาะสม ดำเนินการวิจัยได้ดีและแปรผลการวิจัยได้ถูกต้อง ซึ่งจะทำให้ผู้วิจัยสามารถตอบคำถามวิจัยต่าง ๆ และนำผลการวิจัยไปใช้ในการดูแลรักษาผู้ป่วยได้อย่างเหมาะสม การดูแลรักษาผู้ป่วยจะต้องเลือกใช้การรักษาพยาบาลที่ได้รับการพิสูจน์โดยการวิจัยที่เชื่อถือได้ว่าให้ผลดีมากกว่าผลเสีย ตามหลักการที่ถูกต้องนักวิชาการไม่สามารถเลือกผลงานวิจัยงานใดงานหนึ่งมาตอบคำถามวิจัยนั้นๆ แต่ควรพิจารณาผลงานวิจัยที่มีคุณภาพดีที่เกี่ยวข้องกับเรื่องนั้น ๆ ทั้งหมด และนำเอาข้อมูลมาสังเคราะห์รวมกันโดยใช้การวิจัยเชิงสังเคราะห์ (Research synthesis) ซึ่งประกอบด้วยขั้นตอนที่สำคัญ 2 ขั้นตอน ได้แก่ การทบทวนวรรณกรรมอย่างเป็นระบบ (systematic review) และการวิเคราะห์ข้อมูลแบบ meta-analysis การไม่นำผลการวิจัยเชิงสังเคราะห์มาใช้อาจจะทำให้ผู้ป่วยเสียโอกาสที่จะได้รับการรักษาพยาบาลที่ได้ผลดีหรืออาจจะได้รับการรักษาพยาบาลที่มีผลเสียมากกว่าผลดี อาจจะมีการทำวิจัยที่ไม่จำเป็น เพราะถ้าทำวิจัยเชิงสังเคราะห์โดยใช้งานวิจัยที่มีอยู่ก็จะได้คำตอบโดยไม่ต้องทำวิจัยแล้ว และทำให้เกิดการใช้ทรัพยากรที่มีอยู่จำกัดอย่างไม่มีประสิทธิภาพ

โครงการนี้มีวัตถุประสงค์ที่จะ เพื่อผลิตนักวิจัยด้านวิทยาศาสตร์สุขภาพที่มีความสามารถทั้งด้าน Clinical epidemiology research และ research synthesis ผลิตงานวิจัยแบบนิพนธ์ต้นฉบับ (Original articles) ที่มีคุณภาพสูงเพื่อตีพิมพ์ในวารสารระดับนานาชาติ และงานวิจัยเชิงสังเคราะห์เพื่อตีพิมพ์ใน Cochrane Library รวมทั้งดำเนินการให้มีการนำผลงานวิจัยไปใช้อย่างเป็นรูปธรรม

ในระยะเวลา 3 ปีมีนักวิจัยเข้าร่วมในโครงการจำนวน 39 คน จาก 9 สถาบัน มีผลงานตีพิมพ์ใน International journals จำนวน 24 ฉบับ (เป็นงานวิจัย Original articles และบทความใน international peer-reviewed journals จำนวน 11 เรื่อง และงานวิจัยเชิงสังเคราะห์ใน Cochrane Library จำนวน 13 เรื่อง) และมีการตีพิมพ์ Protocols for Cochrane reviews ใน Cochrane Library อีก 14 เรื่องรวมทั้งได้ดำเนินการให้กระทรวงสาธารณสุขโดยกรมอนามัยประกาศนโยบายนำแนวทางการดูแลผู้ตั้งครรภ์แนวใหม่ซึ่งคณะผู้วิจัยได้ร่วมทำวิจัยกับองค์การอนามัยโลกมาใช้ในประเทศไทย

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 39 researchers from nine institutes involved in the program. There were 11 papers published in international peer-reviewed journals and 13 papers in Cochrane Library. We also published 14 protocols for Cochrane reviews in Cochrane Library. We also managed to convince the Ministry of Public Health to implement the new antenatal care model that we collaborated with the World Health Organization as the national policy.

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

Executive Summary

1. ความสำคัญและที่มาของปัญหา

ระบาดวิทยาคลินิกเป็นวิชาพื้นฐานครอบคลุมถึงระเบียบวิธีวิจัยและชีวสถิติ ความรู้ทางด้านระบาดวิทยาคลินิกจะช่วยให้นักวิจัยสร้างโครงการวิจัยที่เหมาะสม ดำเนินการวิจัยได้ดีและแปรผลการวิจัยได้ถูกต้อง ซึ่งจะทำให้ผู้วิจัยสามารถตอบคำถามวิจัยต่าง ๆ และนำผลการวิจัยไปใช้ในการดูแลรักษาผู้ป่วยได้อย่างเหมาะสม

ผู้ให้การดูแลรักษาผู้ป่วยจะต้องเลือกใช้การรักษาพยาบาลที่ได้รับการพิสูจน์โดยการวิจัยที่เชื่อถือได้ว่าให้ผลดีมากกว่า แต่เดิมเป็นที่ยอมรับว่าการวิจัยแบบ randomized controlled trial (RCT) ที่มีขนาดตัวอย่างเพียงพอเป็นการวิจัยที่ดีที่สุดในการจะตอบคำถามวิจัยชนิดนี้ แต่การทำวิจัยแบบ RCT ต้องการผู้เชี่ยวชาญที่มีความรู้และประสบการณ์ งบประมาณค่อนข้างสูง และใช้ระยะเวลานานกว่าจะได้คำตอบและมักจะต้องเป็นการทำวิจัยแบบสหสถาบัน

ตามหลักการที่ถูกต้องนักวิชาการไม่สามารถเลือกผลงานวิจัยงานใดงานหนึ่งมาตอบคำถามวิจัยนั้นๆ แต่ควรพิจารณาผลงานวิจัยที่มีคุณภาพดีที่เกี่ยวข้องกับเรื่องนั้น ๆ ทั้งหมด และนำเอาข้อมูลมาสังเคราะห์รวมกันโดยใช้การวิจัยเชิงสังเคราะห์ (Research synthesis) ซึ่งประกอบด้วยขั้นตอนที่สำคัญ 2 ขั้นตอนได้แก่ การทบทวนวรรณกรรมอย่างเป็นระบบ (systematic review) และการวิเคราะห์ข้อมูลแบบ meta-analysis เป็นวิธีการที่ใช้สังเคราะห์งานวิจัยตั้งแต่ 2 งานวิจัยขึ้นไปเพื่อสรุปผลหาคำตอบสำหรับคำถามวิจัยแต่ละเรื่อง

ถึงแม้การวิจัยเชิงสังเคราะห์จะไม่ใช่เรื่องใหม่แต่ยังมีนักวิชาการไม่มากนักที่เห็นความสำคัญของการวิจัยแบบนี้ ในการวิจัยทางคลินิกการไม่ทำหรือไม่นำผลการวิจัยเชิงสังเคราะห์มาใช้อาจจะทำให้เกิดผลเสียที่ร้ายแรงได้ ผู้ป่วยอาจเสียโอกาสที่จะได้รับการรักษาพยาบาลที่ได้ผลดี หรืออาจจะได้รับการรักษาพยาบาลที่มีผลเสียมากกว่าผลดี อาจจะมีการทำวิจัยที่ไม่จำเป็นเพราะถ้าทำวิจัยเชิงสังเคราะห์โดยใช้งานวิจัยที่มีอยู่ก็จะได้คำตอบโดยไม่ต้องทำวิจัยแล้ว และทำให้เกิดการใช้ทรัพยากรที่มีอยู่จำกัดอย่างไม่มีประสิทธิภาพ

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 ในประเทศไทยและภูมิภาคเอเชียตะวันออกเฉียงใต้ วัตถุประสงค์ที่สำคัญของ TCN คือสนับสนุนให้มีการใช้และการทำวิจัยเชิงสังเคราะห์กับ 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) จะใช้ระเบียบวิธีวิจัยและวิธีการทางชีวสถิติที่เหมาะสม

3.2 สำหรับการวิจัยเชิงสังเคราะห์จะใช้วิธีการและกลไกของ Cochrane Collaboration

4. ผลการดำเนินงานวิจัย (พ.ศ. 2547-2550)

4.1 มีนักวิจัยเข้าร่วมในโครงการจำนวน 39 คน จาก 9 สถาบัน

4.2 มีผลงานตีพิมพ์ใน international journals จำนวน 24 papers

4.2.1 ตีพิมพ์ผลงานวิจัย Original articles และบทความใน international peer-reviewed journals จำนวน 11 เรื่อง

4.2.2 ตีพิมพ์ผลงานวิจัยเชิงสังเคราะห์ (Cochrane reviews) ใน Cochrane Library จำนวน 13 เรื่อง

4.3 มีการตีพิมพ์ Protocols for Cochrane reviews ใน Cochrane Library จำนวน 14 เรื่อง

4.4 กระทรวงสาธารณสุขโดยกรมอนามัยได้ประกาศนโยบายนำแนวทางการดูแลผู้ตั้งครรภ์แนวใหม่ซึ่งคณะผู้วิจัยได้ร่วมทำวิจัยกับองค์การอนามัยโลกมาใช้ในประเทศไทย โดยในปีพ.ศ. 2551 นี้จะขยายพื้นที่จากที่ได้ดำเนินการที่จังหวัดขอนแก่นแล้วให้ครอบคลุมอีก 5 จังหวัด ได้แก่ กาฬสินธ์ มหาสารคาม เชียงราย ลพบุรี และนครศรีธรรมราช รวมทั้งโรงพยาบาลของศูนย์อนามัยทุกแห่ง

เนื้อหางานวิจัย

การวิจัยในโครงการประกอบด้วยส่วนสำคัญ 2 ส่วน ได้แก่

1. การวิจัยด้านระบาดวิทยาคลินิก (Clinical Epidemiology Research)

เป็นการดำเนินการวิจัยเพื่อตอบปัญหาที่เกี่ยวข้องกับการดูแลรักษาผู้ป่วยโดยใช้ระเบียบวีวิจัยและสถิติที่เหมาะสมได้แก่

1.1 Epidemiology of Rape at Police General Hospital เป็น descriptive study (กำลังรอตีพิมพ์)

1.2 Air and expansible gas in pneumatic retinopexy: A randomized controlled trial (กำลังวิเคราะห์ข้อมูล)

1.3 Protective effect of Depo Medroxyprogesterone Acetate on epithelial ovarian cancer : A multicenter case-control study (กำลังรอตีพิมพ์)

1.4 Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery: A multicenter randomized controlled trial (กำลังดำเนินการ)

นอกจากนี้ยังมีงานวิจัยที่ใช้ข้อมูลจากโครงการที่ดำเนินมาก่อนหน้านี้และนำมาวิเคราะห์และตีพิมพ์ในวารสารนานาชาติ ได้แก่

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2. การวิจัยเชิงสังเคราะห์ (Research synthesis) สมาชิกของกลุ่มได้ร่วมทำการวิจัยเชิงสังเคราะห์ร่วมกับ Cochrane Collaboration ตามระเบียบวิวิจัยเชิงสังเคราะห์ที่เป็นมาตรฐานตามข้อกำหนดของ Cochrane review groups ต่าง ๆ ได้ดำเนินการวิจัยเรียบร้อยและตีพิมพ์ใน Cochrane Library แล้วจำนวน 13 เรื่อง ได้แก่

2.1 Yamasmit W, Chaithongwongwatthana S, Tolosa JE, Limpongsanurak S, Pereira L, **Lumbiganon P.** Prophylactic oral betamimetics for reducing preterm birth in women with a twin pregnancy. Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No.: CD004733.

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2.3 **Krisanaprakornkit T, Krisanaprakornkit W,** Piyavhatkul N, **Laopaiboon M.** Meditation therapy for anxiety disorders. *Cochrane Database of Systematic Reviews* 2006, Issue 1. Art. No.: CD004998.

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2.9 **Lumbiganon P,** Chaikitpinyo A. Antibiotics for brain abscesses in people with cyanotic congenital heart disease. *Cochrane Database of Systematic Reviews* 2007, Issue 3. Art. No.: CD004469.

2.10 **Sinawat S, Buppasiri P, Lumbiganon P, Pattanittum P,** Long versus short course treatment with Metformin and Clomiphene Citrate for ovulation induction in women with PCOS. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No.: CD006226.

2.11 Laupattarakasem W, **Laopaiboon M,** Laupattarakasem P, Sumananont C. Arthroscopic debridement for knee osteoarthritis. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No.: CD005118.

2.12 Panpanich R, Lerttrakarnnon P, **Laopaiboon M.** Azithromycin for acute lower respiratory tract infections. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No.: CD001954.

2.13 **Swadpanich U, Lumbiganon P,** Prasertcharoensook W, **Laopaiboon M.** Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No.: CD006178.

3. ดำเนินการวิจัยเชิงสังเคราะห์ถึงขั้นตอนการตีพิมพ์ Protocol ใน Cochrane Library (เทียบได้กับจัดทำ Research proposal ที่ได้ผ่านการกลั่นกรองและรับรองจาก Cochrane Review Groups ต่าง ๆ แล้วและกำลังทำวิจัยเพื่อให้เป็น Cochrane reviews อีกจำนวน 14 เรื่อง ได้แก่

3.1 **Wongtra-ngan S,** Edi-Osagie EC, Vutyavanich T. Follicular flushing during oocyte retrieval in assisted reproductive techniques. *Cochrane Database of Systematic Reviews* 2004, Issue 1. Art. No.: CD004634.

3.2 **Tangsiriwatthana T, Lumbiganon P, Sawadpanich U, Laopaiboon M.** Paracervical local anaesthesia for cervical dilatation and uterine intervention. *Cochrane Database of Systematic Reviews* 2004, Issue 4. Art. No.: CD005056.

3.3 **Thanaviratananich S,** Watanasapt P, **Laopaiboon M**. Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media. *Cochrane Database of Systematic Reviews* 2004, Issue 4. Art. No.: CD004975.

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3.7 **Krisanaprakornkit T,** Witoonchart C, **Krisanaprakornkit W.** Meditation therapies for attention deficit /hyperactivity disorder. *Cochrane Database of Systematic Reviews* 2007, Issue 2. Art. No.: CD006507.

3.8 **Yospaiboon Y,** Ratanapakorn T. Pars plana vitrectomy for diabetic macular edema. *Cochrane Database of Systematic Reviews* 2007, Issue 2. Art. No.: CD006486.

3.9 **Suwannachat B, Lumbiganon P, Laopaiboon M.** Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery. *Cochrane Database of Systematic Reviews* 2007, Issue 3. Art. No.: CD006636.

3.10 **Boonmak S, Boonmak P, Laopaiboon M.** Deliberate hypotension with propofol under anaesthesia for functional endoscopic sinus surgery (FESS). *Cochrane Database of Systematic Reviews* 2007, Issue 3. Art. No.: CD006623.

3.11 **Krisanaprakornkit W, Krisanaprakornkit T,** Yimyaem PR, Thienthong S, Wongswadiwat M. Pharmacological management for prevention of phantom limb pain. *Cochrane Database of Systematic Reviews* 2007, Issue 3. Art. No.: CD006610.

3.12 **Boonmak P, Boonmak S, Krisanaprakornkit W, Pattanittum P.** High concentration versus low concentration sevoflurane for anaesthesia induction. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No.: CD006837.

3.13 **Laopaiboon M, Lumbiganon P,** Martis R, Vatanasapt, Somchiwong B. Music during caesarean section under regional anesthesia for improving maternal and infant outcomes. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No.: CD006914.

3.14 **Srisubat A,** Potisat S, Lojanapiwat B, Setthawong V, **Laopaiboon M.** Extracorporeal shock wave lithotripsy (ESWL) for kidney stones (Protocol) *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No.: CD007044.

Outputs ที่ได้จากโครงการ (2547-2550)

1. ตีพิมพ์ผลงานวิจัย Original articles และบทความใน international peer-reviewed journals จำนวน 11 เรื่อง (กรุณาดูรายละเอียดในภาคผนวกที่ 1)

2. ตีพิมพ์ผลงานวิจัยเชิงสังเคราะห์ (Cochrane reviews) ใน Cochrane Library จำนวน 13 เรื่อง (กรุณาดูรายละเอียดในภาคผนวกที่ 2)

3. มีนักวิจัยเข้าร่วมในโครงการจำนวน 39 คน จาก 9 สถาบัน (กรุณาดูรายละเอียดในภาคผนวกที่ 3)

4. ประเทศไทยมีโครงการวิจัยเชิงสังเคราะห์ที่ทำร่วมกับ Cochrane Collaboration มากขึ้นอย่างรวดเร็วและปัจจุบันเป็นอันดับที่ 3 ใน Asia รองจาก จีนและอินเดียเท่านั้น (กรุณาดูเอกสารในภาคผนวกที่ 4)

5. ผลงานวิจัยเรื่องการดูแลผู้ตั้งครรภ์แนวใหม่ขององค์การอนามัยโลก ซึ่งหัวหน้าโครงการ (ศ.น.พ.ภิเศก ลุมพิกานนท์) ได้ร่วมในการทำวิจัยกับองค์การอนามัยโลกตั้งแต่แรก ได้เผยแพร่โดยการตีพิมพ์ในวารสาร Lancet และองค์การอนามัยโลกได้ออกเอกสาร Manual for Implementation แนะนำให้ประเทศสมาชิกทั่วโลกนำไปใช้ดูแลผู้ตั้งครรภ์ ต่อมาได้นำผลมาใช้ดูแลผู้ตั้งครรภ์ในจังหวัดขอนแก่น และในปี 2551 นี้ ท่านอธิบดีกรมอนามัย และ ฯพณฯ รัฐมนตรีว่าการกระทรวงสาธารณสุขได้ประกาศนโยบายที่จะขยายการดูแลผู้ตั้งครรภ์แนวใหม่ดังกล่าวไปใช้ในโรงพยาบาลศูนย์อนามัยทุกแห่งและในอีก 5 จังหวัด ได้แก่ เชียงราย ลพบุรี นครศรีธรรมราช กาฬสินธุ์ และมหาสารคาม (กรุณาดูเอกสารในภาคผนวกที่ 5)

6. ตีพิมพ์ Protocols for Cochrane reviews ใน Cochrane Library จำนวน 14 เรื่อง (กรุณาดูรายละเอียดในภาคผนวกที่ 6)

7. งานวิจัยที่ได้ตีพิมพ์ใน international peer-review journals และ Cochrane Library ได้นำไปอ้างถึงในวารสารต่างประเทศ จำนวน 62 ครั้ง (กรุณาดูรายละเอียดในภาคผนวกที่ 7)

8. เรียบเรียงหนังสือ สูติศาสตร์เชิงประจักษ์ (Evidence-Based Obstetrics) จัดพิมพ์เผยแพร่ไปตามห้องสมุดคณะแพทยศาสตร์ทุกแห่ง โรงพยาบาลศูนย์ และโรงพยาบาลทั่วไปของกระทรวงสาธารณสุขทุกแห่ง ศูนย์อนามัยของกรมอนามัยทุกศูนย์ และได้นำขึ้น Web Site โครงการสายใยรักของกรมอนามัย โดยได้รับอนุญาตจาก สำนักงานกองทุนสนับสนุนการวิจัย (สกว.) http://bflh.anamai.moph.go.th/back-office/upload/document/สูติศาสตร์เชิงประจักษ์.pdf และ Web Site ภาควิชาสูติศาสตร์และนรีเวชวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น http://obgyn1.md.kku.ac.th/site_data/mykku_obgyn1/13/obgyn.pdf

From research to practice: the example of antenatal care in Thailand

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Abstract The rationale for providing antenatal care is to screen predominantly healthy pregnant women to detect early signs of, or risk factors for, abnormal conditions or diseases and to follow this detection with effective and timely intervention. The recommended antenatal care programme in most developing countries is often the same as the programmes used in developed countries. However, in developing countries there is wide variation in the proportion of women who receive antenatal care. The WHO randomized trial of antenatal care and the WHO systematic review indicated that a model of care that provided fewer antenatal visits could be introduced into clinical practice without causing adverse consequences to the woman or the fetus. This new model of antenatal care is being implemented in Thailand. Action has been required at all levels of the health-care system, from consumers through to health professionals, the Ministry of Public Health and international organizations. The Thai experience is a good example of moving research findings into practice, and it should be replicated elsewhere to effectively manage other health problems.

Keywords Prenatal care/organization and administration; National health programs/organization and administration; Randomized controlled trials; Meta-analysis; World Health Organization; Evidence-based medicine; Thailand (*source: MeSH, NLM*).

Mots clés Soins prénataux/organisation et administration; Programme national santé/organisation et administration; Essai clinique randomisé; Méta-analyse; Organisation mondiale de la Santé; Médecine factuelle; Thaïlande (*source: MeSH, INSERM*).

Palabras clave Atención prenatal/organización e administración; Programas nacionales de salud/organización e administración; Ensayos controlados aleatorios; Meta-análisis; Organización Mundial de la Salud; Medicina basada en evidencia; Tailandia (*fuente: DeCS, BIREME*).

الكلمات المفتاحية: الرعاية السابقة للولادة، تنظيم وإدارة الرعاية السابقة للولادة؛ البرامج الصحية الوطنية، تنظيم وإدارة البرامج الصحية الوطنية؛ التجارب المعشاة المضبوطة بالشواهد؛ التحليل التلوي؛ منظمة الصحة العالمية؛ الطب المسند بالبينات؛ تايلاند (**المصدر**: **رؤوس الموضوعات الطبية المكتب الإقليمي لشرق المتوسط**)

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Voir page xxx le résumé en français. En la página xxx figura un resumen en español.

What is antenatal care?

In theory, antenatal care reduces maternal and perinatal morbidity and mortality directly through the detection and treatment of pregnancy-related or intercurrent illness or indirectly through the detection of women at increased risk of complications of delivery by ensuring that they are cared for in a suitably equipped facility (*1*). The basic content of care at each visit has not changed substantially over the years, although modern technology has led to the introduction of several new elements in pregnancy surveillance (*2*).

As maternal and perinatal outcomes improved dramatically in the developed world, antenatal care was given much of the credit despite a lack of evidence for its precise benefits (*3*). In countries where women usually attend antenatal services early in pregnancy, the average number of visits is 10–12, and attendance rates are nearly 100% (*4*). Recently, trials have indicated that reducing the number of antenatal visits does not affect overall outcome (*5–8*).

In developing countries, where 80% of the world's women live, the process of pregnancy and childbirth is still sometimes quite dangerous (*9*). The recommended programmes of antenatal care in most developing countries are often similar to those used in developed countries. However, departure from the standard programme is almost always the rule, usually the result of insufficient resources or women's lack of attendance (*10*). Surveys from a number of developing countries done between 1980 and 1989 revealed that coverage of antenatal care ranged from 50% to 90% (*11*).

Evidence supporting the effectiveness of antenatal care

Questions about the effectiveness of antenatal care were initially raised by Archie Cochrane in 1972. He wrote: "By some curious chance, antenatal care has escaped the critical assessment to which most screening procedures have been subjected" (*12*). Before the WHO antenatal care trial was conducted, there had been attempts to evaluate antenatal care programmes for low-risk women. Fiscella found that the absence of direct, randomized controlled trials precluded a straightforward evaluation of

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the impact of prenatal care on birth outcomes (*13*). Another extensive review of the literature found that "carefully controlled evaluations of the content, number and timing of prenatal care visits for women with differing medical and social risks are essential" (*14*).

WHO antenatal care trial and research synthesis

The Department of Reproductive Health and Research at WHO conducted a multicentre cluster–randomized controlled trial to evaluate routine antenatal care in developing countries (*15*). A total of 53 antenatal care clinics in Argentina, Cuba, Saudi Arabia and Thailand were randomly assigned to provide either the new WHO model of care or the standard model used in that country. Altogether, 27 clinics were assigned to use the new model and 26 clinics to use the standard model. In total, 24 678 women were enrolled over an 18-month period between 1996 and 1998. Women attending the clinics that had been randomly assigned to use the new model had a median of five visits; those visiting clinics providing standard care had a median of eight visits. The trial found that providing routine antenatal care using the new model produced similar maternal and perinatal outcomes to the standard model. Women and providers seemed to accept the new model, and it was found that implementation may reduce the costs of antenatal care (*15*).

A systematic review of randomized controlled trials evaluating the effectiveness of different models of antenatal care was published by WHO in 2001 (*16*, *17*). There was no difference between the two models with respect to the incidence of pre-eclampsia, urinary-tract infections, postpartum anaemia and maternal mortality. The two models were also similar in terms of the incidence of children born at low birth weight and perinatal mortality. Some women in the studies, especially those in developed countries, expressed dissatisfaction with the reduced number of antenatal visits. The new model, under which women had fewer antenatal visits, cost the same or less than the standard model.

Based on these results and the results of the randomized trial of antenatal care, it was concluded that models with fewer antenatal visits could be introduced into clinical practice in both developed and developing countries without any risk of adverse consequences to the woman or fetus. WHO has since published *The WHO antenatal care randomized trial: manual for the implementation of the new model* and distributed it worldwide (*18*).

Implementing the new model for antenatal care in Thailand

There are often unacceptable delays in implementing research findings. This results in inappropriate care for patients (*19*). Three basic issues influence the uptake of research evidence: the attributes of the evidence, barriers and facilitators to changing practices, and the effectiveness of dissemination and implementation strategies (*20*). Evidence on the effectiveness of using specific interventions to promote change is incomplete, but a combination of interventions is often needed (*21*). It is possible to change the behaviour of health-care providers but this change generally requires the use of comprehensive approaches that are tailored to specific settings and target groups (*20*). Passive dissemination is generally ineffective (*22*). Researchers need to design studies that take into account how and by whom the results will be used (*23*), and they must also be aware of the need to convince decision-makers to use the intervention (*23*).

As participants in the WHO antenatal care trial we were cognizant of the difficulties of bringing research into practice, so we developed an implementation plan for the new antenatal care model in Thailand before the trial started.. At the central level, we informed authorities in the Ministry of Public Health, including the Director of the Division of Health Promotion and the Director-General of the Department of Health, about the trial. They were interested in the trial and eager to be kept informed about its progress and the results. We obtained ethical approval from the Ethics Committee of the Ministry of Public Health. At the local level, we obtained permission to conduct the study from the Director of the Regional Health Promotion Centre and the Provincial Chief Medical Officer. We also obtained ethical approval from the Ethics Committee of Khon Kaen University.

There are four broad principles of a truly cooperative research partnership: mutual trust and shared decision-making, national ownership, an emphasis on bringing research findings into policy and practice, and the need to develop national research capacity (*24*). To try to build this type of partnership to ensure that our findings would be implemented, we invited medical officers from the Regional Health Promotion Centres and the Provincial Health Office to participate as co-investigators. We created a sense of ownership for the medical officers by including them on the team from the beginning. We strongly believed that this would be one of the crucial steps in getting the research results implemented. The overall WHO antenatal care trial involved people from many organizations (for example, universities, health promotion centres, provincial health offices and district hospitals) and thus helped build research capacity in the countries taking part.

Disseminating the findings of the WHO systematic review to policy-makers, health professionals and consumers was seen as an essential prerequisite to changing practices (*25*). This is because action is required at all levels of health-care systems, from consumers through to health professionals, ministries of health and international organizations (*25*). Therefore, the other important step in implementation was translating the WHO manual into Thai to overcome the language barrier. We presented a translated version of the manual together with copies of the two papers from the Lancet (*16*, *17*) to obtain approval from the relevant public bodies to implement the new antenatal care model in Thailand. We also obtained official permission to implement the new model in Khon Kaen Province from the Governor, the Maternal and Child Health Board and the Administrative Committee for Health Care of the Province.

Once we had obtained approval, we conducted four workshops for 155 health personnel from the 24 Ministry of Public Health hospitals in Khon Kaen Province. We presented participants with the concepts and details of the steps in the new model. We organized a press conference, which was chaired by the Provincial Chief Medical Officer, to inform the media about the rationale behind the model and the implementation of it. We also made two site visits to each hospital to supervise and answer any questions that health personnel might have during implementation.

As of May 2004, the new model had been implemented in all 24 hospitals in Khon Kaen Province that had been included in the workshops. There were some minor problems

during the early phase of implementation. These included the fact that some providers did not want to change from a familiar practice to an unfamiliar one; some providers were not comfortable or did not have enough skills to manage some of the procedures (for example, nurses were not comfortable doing routine pelvic examinations and doctors did not know how to perform external cephalic version); some hospital directors did not want to invest in procedures that they thought were not cost-effective (for example, Rh screening and urine dipsticks); some providers did not follow the recommended steps strictly (for example, the use of classifying forms and checklists); some women were concerned about the long intervals between visits, particularly women who had been pregnant before and who were familiar with having shorter intervals. However, most of these problems were detected, clarified and resolved during the site visits. ■

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Résumé

De la recherche à la pratique : l'exemple des soins anténataux en Thaïlande

Pour justifier l'apport de soins anténataux, on avance la nécessité de soumettre les femmes enceintes essentiellement en bonne santé à un dépistage destiné à détecter les signes précoces, ou les facteurs de risque, d'états anormaux ou de maladies, et de faire suivre cette détection d'une intervention efficace et en temps utile. Le programme de soins anténataux recommandé dans les pays en développement est souvent le même que celui appliqué dans les pays développés. Dans les pays en développement cependant, la proportion de femmes qui reçoivent les soins anténataux est soumise à de grandes variations. D'après l'essai randomisé OMS sur les soins anténataux et la revue systématique de l'OMS, il serait possible d'introduire dans la pratique clinique un modèle de soins prévoyant un moins grand nombre de visites prénatales, sans que cela porte préjudice à la femme ou au fœtus. Ce nouveau modèle de soins anténataux est en cours d'introduction en Thaïlande. Il a nécessité une action à tous les niveaux du système de santé, des consommateurs aux professionnels de santé, au Ministère de la santé publique et aux organisations internationales. L'expérience thaïlandaise est un bon exemple de mise en application pratique des résultats de la recherche et devrait être reproduite ailleurs pour gérer efficacement d'autres problèmes sanitaires.

Resumen

De las investigaciones a la práctica: el ejemplo de la atención prenatal en Tailandia

La finalidad de la prestación de atención prenatal es someter a cribado a las mujeres embarazadas, en su mayoría sanas, para detectar tempranamente los signos o los factores de riesgo de anomalías o enfermedades y responder tras esa detección con una intervención eficaz y oportuna. El programa de atención prenatal recomendado en la mayoría de los países en desarrollo suele coincidir con los programas aplicados en los países desarrollados. Sin embargo, en los primeros la proporción de mujeres que reciben atención prenatal es muy variable. El ensayo aleatorizado de atención prenatal de la OMS y el examen sistemático de la OMS mostraron que es posible introducir en la práctica clínica un modelo de atención que requiera menos visitas prenatales sin perjuicio alguno para la mujer o el feto. En Tailandia se está aplicando este nuevo modelo de atención prenatal, para lo cual ha habido que adoptar medidas a todos los niveles del sistema de salud, desde los consumidores hasta los profesionales sanitarios, el Ministerio de Salud Pública y las organizaciones internacionales. La experiencia de Tailandia ejemplifica la idea de llevar a la práctica los resultados de las investigaciones, y debería reproducirse en otros lugares a fin de gestionar eficazmente otros problemas de salud.

ملخص

من البحوث إلى الممارسة: مثال على الرعاية السابقة للولادة في تايلاند

الخلاصة: إن الأســـاس المنطقي لإيتاء الرعاية في الفترة الســـابقة للولادة هو تحري النســـاء الحوامل اللاتي يتمتعن في أغلب الأحيان بصحة جيدة، وذلك لاكتشاف العلامات الباكرة للحالات غير السوية أو للأمراض، أو لاكتشاف عـــوامل الخطر المرتبطة بهذه الحالات أو الأمراض، وكذلك للقيام بالتدخلات الفعالة في الوقت المناســـب لدى اكتشاف هذه العلامات أو عوامل الخطر. ويغلب أن تتماثل برامج الرعاية الموصى بها في الفترة السابقة للولادة في البلدان النامية والبلدان المتقدمة، إلا أن البلدان النامية تعاني من اختلاف واسع الـنطاق في نسبة النساء اللاتي يتلقين الرعاية السابقة للولادة. وتشير التجارب المعشاة والمراجعات المنهجيـــة التي أجرتها منظمة الصحة العالمية حول الرعاية السابقة للولادة، إلى أن نموذج الرعاية الذي يشتمل على عدد أقل من زيارات الحوامل لمرافق الرعاية الســـابقة للولادة يمكن إدخاله في الممارســـة السريرية (الإكلينيكية) دون أن يسبب ذلك أي عواقب ضائرة للأم أو جنينها. وينفذ حاليا هذا النموذج الجديد من الرعاية الســـابقة للولادة في تايلاند. ويتطلب ذلك القيام بإجراءات على جميع مستويات نظام الرعاية الصحيـــة، بدءاً من متلقي الرعايـــة إلى العاملين الصحيين إلى وزارة الصحة العمومية إلى المنظمات الدولية. وتعد التجربة التي خاضتها تايلاند مثالاً جيداً على تحويل البحوث ونتائجها إلى حيِّز التطبيق والممارسة، وينبغي تكرارها في أماكن أخرى للوصول إلى التدبير الفعال لمشاكل صحية أخرى.

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CORRESPONDENCE

Clinical Trial Registration

TO THE EDITOR: The statement from the International Committee of Medical Journal Editors (ICMJE) with respect to the registration of clinical trials (Sept. 16 issue)[1] advocates the use of www.clinicaltrials.gov as a registry. I am astonished by this recommendation because that registry does not fulfill the criteria demanded by the ICMJE. Currently, only the U.S. federal agencies conducting or sponsoring clinical research and holders of an investigational-new-drug application under U.S. Food and Drug Administration regulations may apply for registration. In contrast, www.controlled-trials.com, an international registry, is open to every investigator. That the editors do not mention this registry amazes me even more because several of them are European. The European guidelines on application for approval by competent authorities and ethics committees before commencement of a clinical trial of medicinal products include detailed instructions for application forms that are used in the member states of the European Union. These application forms ask for the International Standard Randomised Controlled Trial Number (ISRCTN), which to my knowledge is given only in the registry at www.controlled-trials.com. The editors should clarify these contradictions.

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1. DeAngelis C, Drazen JM, Frizelle FA, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. N Engl J Med 2004;351:1250-1.

Editor's note: Since this letter was written clinicaltrials.gov has been opened to any investigator in the world.

TO THE EDITOR: The ICMJE supports a solution to the selective reporting of clinical studies. Although efforts have been made to encourage investigators to register their trials, registration is still voluntary. Several major barriers to the development of a comprehensive registry of clinical trials have been described.[1] Research involving human subjects poses complex ethical issues. As stated by the ICMJE, patients who volunteer to participate in clinical trials deserve to know that their contribution to the improvement of human health will be available to inform health care decisions. Therefore, prospective trial registration is an ethical obligation and should be a legally required component of written informed consent.

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TO THE EDITOR: The trial-registration initiative of the ICMJE is laudable. However, research sponsors are not the only stakeholders who may lose a competitive edge through registration. Researchers from

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developing countries are at a disadvantage too. The timely completion and publication of research with limited resources and limited infrastructure already constitute a tall order.[1,2] A registration process that includes immediate disclosure of research information could further retard the limited competitiveness of the developing world. What might be done is to have trials registered at the outset, but without the information being publicly accessible for a certain grace period. This approach would ensure transparency but would not compromise any competitive edge to which researchers who painstakingly design an innovative study are entitled.

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Chronic Renal Disease and Cardiovascular Risk

TO THE EDITOR: Go et al. (Sept. 23 issue)[1] estimated the glomerular filtration rate (GFR) with the simplified four-variable Modification of Diet in Renal Disease (MDRD) formula. Almost half the subjects in their study population (41.7 percent) did not describe themselves as black or white. Despite the important influence of a person's ethnic background on the estimated GFR, the variable "race or ethnic background" allows only factors for "European-American" or "African-American" to be inserted into the MDRD formula.[2] It can be assumed that if more accurate estimates of the GFR had been obtained with the use of modified ethnicity-specific multiplication factors (e.g., for Asians), the conclusions of the study would probably not have differed. However, it is important to emphasize that the MDRD formula still awaits validation in several nonblack, nonwhite populations living throughout the United States and elsewhere in the world.

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TO THE EDITOR: In the studies by Go et al. and Anavekar et al.,[1] mild renal disease was associated with death and cardiovascular events. Two issues were not discussed. The first is that the MDRD equation has not been tested in elderly persons or in persons with reduced muscle mass.[2] Both studies, however, included a high percentage of older adults, and there was no adjustment for body-mass index. Their conclusions may have been weakened as a result. The second is that neither of the two studies showed the size of the effect of mild renal disease on death and cardiovascular events. The size of the effect in an observational study is important.[3] Many traditional risk factors, such as hypertension and diabetes, varied significantly according to the GFR, and adjustments for these factors were made. It is still unclear to what extent mild renal disease contributed to death and cardiovascular events. Finally, the GFR tended to decline with increasing age in the study by Anavekar et al. but not in the study by Go et al.

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DR. GO AND COLLEAGUES REPLY: Dr. Risch and colleagues note that some members of our cohort could not be determined to be either black or white because either those subjects were of another race

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Preeclampsia, gestational hypertension and intrauterine growth restriction, related or independent conditions?

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KEY WORDS
Preeclampsia
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Objective: Preeclampsia, gestational hypertension, and unexplained intrauterine growth restriction may have similar determinants and consequences. In this study, we compared determinants and perinatal outcomes associated with these obstetric conditions.

Study design: We analyzed 39,615 pregnancies (data from the WHO Antenatal Care Trial), of which 2.2% were complicated by preeclampsia, 7.0% by gestational hypertension, and 8.1% by unexplained intrauterine growth restriction (ie, not associated with maternal smoking,

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The views expressed in this document are solely the responsibility of the authors and do not necessarily represent the views of the World Health Organization or its Member States.

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maternal undernutrition, preeclampsia, gestational hypertension, or congenital malformations). We compared the risk factors associated with these groups. Fetal death, preterm delivery, and severe neonatal morbidity and mortality were the primary outcomes. Logistic regression analyses were adjusted for study site, socioeconomic status, and (if appropriate) birth weight and gestational age.

Results: Diabetes, renal or cardiac disease, previous preeclampsia, urinary tract infection, high maternal age, twin pregnancy, and obesity increased the risk of both hypertensive conditions. Previous large-for-age birth, reproductive tract surgery, antepartum hemorrhage and reproductive tract infection increased the risk for gestational hypertension only. Independent of maternal age, primiparity was a risk factor only for preeclampsia. Both preeclampsia and gestational hypertension were associated with increased risk for fetal death and severe neonatal morbidity and mortality. Mothers with preeclampsia compared with those with unexplained intrauterine growth restriction were more likely to have a history of diabetes, renal or cardiac disease, chronic hypertension, previous preeclampsia, body mass index more than 30 kg/cm^2, urinary tract infection and extremes of maternal age. Conversely, unexplained intrauterine growth restriction was associated with higher risk of low birth weight in previous pregnancies, but not with previous preeclampsia. Both conditions increased the risk for perinatal outcomes independently but preeclampsia was associated with considerable higher risk.

Conclusion: Preeclampsia and gestational hypertension shared many risk factors, although there are differences that need further evaluation. Both conditions significantly increased morbidity and mortality. Conversely, preeclampsia and unexplained intrauterine growth restriction, often assumed to be related to placental insufficiency, seem to be independent biologic entities.

Hypertension complicates approximately 9% of all pregnancies with preeclampsia-eclampsia (up to 4%) being a major cause of maternal and perinatal morbidity and mortality.[1] Currently, preeclampsia (de novo hypertension after mid pregnancy plus new-onset proteinuria) and gestational hypertension (de novo hypertension after mid pregnancy but no proteinuria) are considered either separate diseases affecting similar organs[2] or different severities of the same underlying disorder. According to the latter hypothesis, gestational hypertension is merely an early or mild stage of preeclampsia, perhaps preceding renal involvement and thus proteinuria.

Intrauterine growth restriction (IUGR), as reflected by small for gestational age (SGA), of diverse causes, affects a fair number of newborn infants worldwide, mainly in developing countries.[3] Some forms of IUGR have been etiologically linked to preeclampsia, based on similar placental disease described as abnormal implantation and characterized by failure of trophoblasts to differentiate, to invade, and to remodel the spiral arteries.[4] These similarities underlie the hypothesis that preeclampsia and IUGR secondary to placental insufficiency share cause but have different clinical manifestations.[5]

Obviously, a clearer understanding of each of the 3 disorders described previously is a goal of studies that examine, whether they share a common cause. Such studies were recently recommended[6] and should lead to improved methods of prevention, detection, and treatment. The presence of the large database from our "WHO multicentre randomized trial evaluating a new model of antenatal care,"[7] provided an opportunity to compare preeclampsia, gestational hypertension, and IUGR in terms of risk or protective factors and immediate perinatal outcomes.

Material and methods

This is a secondary analysis of data collected in the World Health Organization (WHO) Antenatal Care Trial.[7] This trial using a cluster randomization design (the clusters being the antenatal care clinics) was conducted in Rosario, Argentina, Havana, Cuba, Jeddah, Saudi Arabia, and Khon Kaen, Thailand. It enrolled 24,678 women in 53 antenatal clinics and took place between August 1996 and December 1998. In addition, data from 5 hospitals (17,073 pregnant women) affiliated to 1 of the participating centers (the Centro Rosarino de Estudios Perinatales CREP, Rosario, Argentina), that applied all the trial's data collection procedures to their entire pregnant population during the same study period, were also available for analysis. This complete data set has been recently used for another observational study.[8]

All study clinics had a standard antenatal care system following protocols and predefined activities, including procedures for glucose tolerance test, as well as screening and treatment for urinary and reproductive tract infections. All data were extracted prospectively from medical records available at all the participating clinics and hospitals.

The original trial, its population and primary outcomes are described in detail in the literature.[7,8] Of

relevance to the current analysis, the incidences of preeclampsia, SGA, neonatal mortality and neonatal intensive care unit stay more than 7 days were evaluated by using the χ^2 test for heterogeneity and did not differ among participating countries.[8] Baseline characteristics between the 2 groups in the original trial were similar in terms of demographic and obstetric characteristics.[7] The 2 arms of the original trial had similar rates of most of perinatal outcomes without reaching statistical significant levels, including preeclampsia/eclampsia and IUGR.

The *best obstetric estimate* of gestational age was determined as outlined in the WHO Trial Manual[9] including ultrasound examination if requested by the attending staff to corroborate uncertain gestational age.[8] Preeclampsia was defined as de novo hypertension (blood pressure $\geq$140 mm Hg systolic or $\geq$90 mm Hg diastolic after mid pregnancy plus proteinuria $\geq$2+ on qualitative examination [dipstick] or 300 mg or more in a 24-hour urine sample) and was restricted to cases of preeclampsia-eclampsia occurring anytime during pregnancy and up to 24 hours postpartum.[7,8] Gestational hypertension was defined as de novo hypertension as above after mid pregnancy and no proteinuria.

In the original trial, the new model conducted routine urinary screening with dipstick for proteinuria. Although, as we have discussed in previous publications, there was no significant different rate of detection of preeclampsia, we have adjusted for treatment group in all the analyses by adding to all regression models a variable indicating the treatment group of the original trial.

IUGR was diagnosed, when birth weight was below the 10th percentile of that anticipated for gestational age.[8,10] We selected this fetal growth chart recommended by WHO for international comparisons, and it is the same we used in previous analyses of this data set.[7] Socioeconomical status for each woman was evaluated by using an index derived from statistical analysis, including maternal education, marital status, and house characteristics.

Other essentials of the original trial included data forms translated and adapted to local terminology and practice, trained female interviewers who abstracted information, and if needed, queried mothers during the postpartum period and a data quality-monitoring unit at each research center.[11] The participating staff, while aware that a trial was being conducted, was not informed of the specific hypotheses being tested. Finally, unknown to its clinic staff, each center was audited twice by external supervisors, acquiring a random sample of 759 women, that when analyzed by kappa statistics validated the agreement between observers during data acquisition.[7,8] Kappa statistics were 0.93 or higher for birth weight, preeclampsia and maternal morbidity; 0.90 for gestational hypertension and 0.97 for IUGR. Kappa statistics for baseline characteristics were 0.79 or higher. The intraclass correlation coefficient for gestational age at birth was 0.93 and 0.99 for birth weight.

Data from 41,751 pregnant women were initially available for analysis; 929 women, who delivered before gestational week 22, or whose newborn infant weighed less than 500 g were excluded, as were 741 women lost to follow-up, leaving data from 40,081 births. We further excluded 466 newborn infants with clinical evidence of congenital malformations or structural defects (Figure). We calculated the rate of multiple pregnancies by study group; however, for the analysis of risk factors and outcomes, we selected the first-born infant and considered the pregnancy as singleton. The final analysis population was 39,615 women and their pregnancies.

For the current analysis, the study population was classified according to presence of preeclampsia/eclampsia, gestational hypertension, and IUGR; pregnancies with combinations of these entities were also identified. IUGR in the presence of either preeclampsia and/or gestational hypertension was considered secondary to the hypertensive condition, and these cases were analyzed within those groups. Women without any of these conditions constituted the reference group.

IUGR newborns were further divided in terms of perceived cause or risk factors into 4 subgroups: (1) IUGR associated with smoking, (2) IUGR associated with undernutrition (defined as a maternal body mass index [BMI] $<$19.8 kg/m^2 and/or severe anaemia in pregnancy $<$9.0 g/L of hemoglobin), (3) IUGR secondary to preeclampsia or gestational hypertension, and (4) all the remaining IUGR cases without congenital malformations were considered unexplained IUGR. All study groups are mutually exclusives and each woman was included only in 1 of them. The unexplained IUGR group was further evaluated by selecting newborn infants with a birth weight below the 5th percentile for gestational age derived from the same fetal growth chart.[10]

We defined *determinants* for the conditions studied, a series of sociodemographic characteristics, elements in the pregnancy history, medical, and obstetric complications of current pregnancy and compared them among preeclamptic, gestational hypertension, and unexplained IUGR groups. IUGR secondary to preeclampsia is not considered in the latter group, but included in the preeclampsia group.

Perinatal outcomes were fetal death, preterm delivery, newborn length of stay at the neonatal intensive care unit (NICU) or other special care unit for 7 days or more (used as a proxy indicator for severe neonatal morbidity) and neonatal death until hospital discharge. For the rate of days of stay in the NICU, the denominator was all newborn infants who survived the first week of life. Finally, we also compared perinatal outcomes among IUGR infants born to mothers with preeclampsia or gestational hypertension with unexplained IUGR.

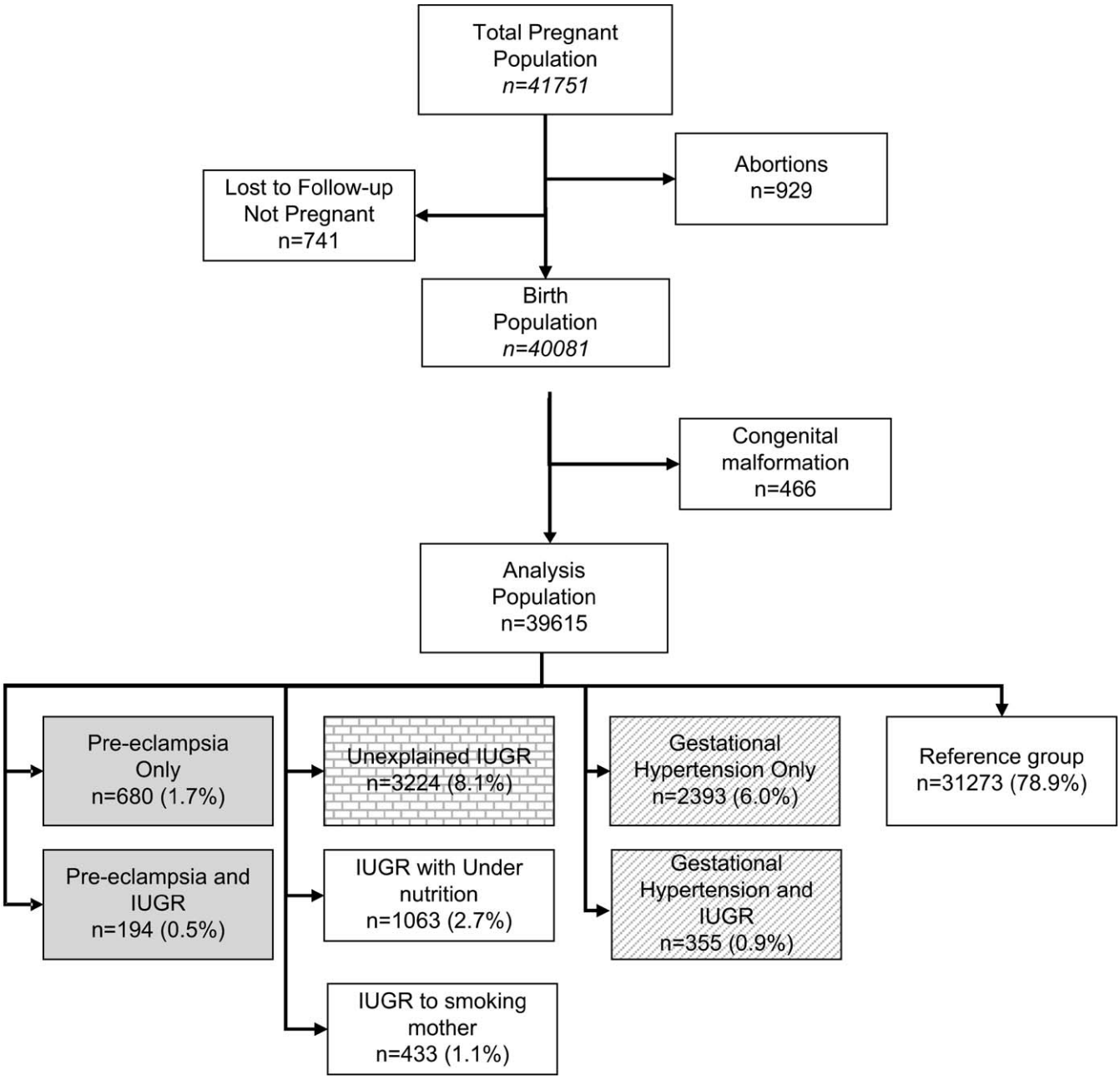

Figure Study population flow chart. During the analysis comparisons were made between: (1) Preeclampsia ▭ vs gestational hypertension ▨ compared with reference group ▭ and (2) preeclampsia ▭ vs unexplained IUGR ▤ compared with reference group ▭. All study groups are mutually exclusives; each woman was included in only one of these groups.

The proportion of cases with preeclampsia, gestational hypertension, and IUGR was estimated as a fraction of the total study population. Risk factors were compared by computing the proportion of subjects in each study group. A separate multinomial logit model[12,13] was developed for each risk factor, considering study group as dependent variable and adjusting for possible confounders. All regression models included socioeconomic status (SES) and study site. From these models, adjusted odds ratios (OR) with their corresponding 95% CI were obtained for the risk factors in the preeclampsia and gestational hypertension groups compared with the reference group. A similar approach was carried out for comparing preeclampsia and unexplained IUGR with the reference group.

Logistic regression models[12] were used to analyze the relationships between preeclampsia, gestational hypertension and IUGR groups with perinatal outcomes. ORs derived from these models were adjusted by study site, treatment group in the original trial, and SES. Birth weight and gestational age were included in the analysis comparing outcomes for the preeclampsia and

gestational hypertension groups. The linearity assumption for the continuous variables was evaluated, and nonlinear terms were used to improve the goodness of fit (Hosmer-Lemeshow statistics).[12]

All protocols were approved by the WHO Committee for Research into Human Subjects and the Institutional Review Boards of the participating institutions. Analyses were made with SAS software version 8.2 (SAS, Cary, NC).

Results

The Figure depicts the study population. The incidence of preeclampsia was 2.2% (0.5% associated with IUGR) and that of gestational hypertension 7.0%, (0.9% associated with IUGR). The total incidence of IUGR was 13.3%. In addition to the 1.4% secondary to preeclampsia or gestational hypertension, 1.1% of the IUGR cases were associated with smoking, 2.7% with undernutrition, and 8.1% categorized as unexplained IUGR. The incidence of IUGR among preeclamptic women was 22.2%, and among women with gestational hypertension was 13%.

Do preeclampsia and gestational hypertension share similar risk factors?

Table I depicts rates and ORs (95% CI) comparing all women with preeclampsia or gestational hypertension with the reference group. Both gestational hypertension and preeclampsia were associated with a host of risk factors when compared with the reference group. Diabetes, renal or cardiac disease, preeclampsia in the previous pregnancy, urinary tract infection, high maternal age, twin pregnancy, or obesity increased the risk of both hypertensive conditions. SES was similarly distributed in these conditions (Table I).

Previous large-for-gestational-age (LGA) birth, history of reproductive tract surgery, antepartum hemorrhage, and reproductive tract infection increased the risk for gestational hypetension only. After adjusting for young maternal age (<16 years), primiparity remained as independent risk factor for preeclampsia, but only marginally for gestational hypertension. Interestingly, history of chronic respiratory conditions was independently associated with preeclampsia but not with gestational hypertension (Table I). Unfortunately, we did not have information related to any medication taken for treatment of respiratory ailments.

Do pregnancies complicated by preeclampsia and gestational hypertension have similar perinatal outcomes?

Women with gestational hypertension had a mean birth weight and gestational age similar to those of the reference group. Women with preeclampsia had a lower mean gestational age (37.5 weeks) and mean birth weight (2845 g), than those in the reference and gestational hypertension groups (Table II).

Fetal death was significantly higher in the preeclampsia group 2.2%, compared with either the gestational hypertension (1.4%), or reference (0.9%) groups. ORs adjusted for site and SES were 2.5 (95% CI 1.6-4.1) in the preeclampsia group and OR 1.6 (95% CI 1.1-2.3) in the gestational hypertension group, when compared with the reference group (Table III).

The rate of preterm delivery in preeclamptic women (27.4%) was significantly higher than in women in gestational hypertension (11.0%) or in the reference (8.8%) groups (preeclampsia, adjusted OR = 3.8; 95% CI 3.3-4.5; gestational hypertension, adjusted OR = 1.2; 95% CI 1.1-1.4). Importantly, the rate of very early preterm delivery was 4.8% for preeclampsia, higher than that of the gestational hypertension (1.1%) and the reference (1.6%) groups (Table III). Among preeclamptic women, 74% of the preterm deliveries were medically indicated, compared with 39% in women with gestational hypertensions and 6.8% in the reference group (data not shown in table). The crude ORs for fetal death, preterm delivery, and very early preterm delivery were similar to the adjusted ORs for all groups (Table III).

Table III also presents crude and adjusted ORs for neonatal morbidity and mortality. In the crude analysis, preeclampsia increased the odds 6.0-fold for NICU stay 7 days or longer and 4.6-fold for neonatal death versus the reference group. Gestational hypertension also significantly increased the odds for these 2 outcomes, but in a smaller magnitude. Adjusting for birth weight (the most important variable), SES, treatment group of the original trial and geographical area, the increased odds for preeclampsia was smaller, OR = 1.5 (95% CI 1.2-2.0) for NICU stay 7 days or longer and disappears for neonatal death (OR = 0.9; 95% CI 0.5-1.8) (Table III). Similar adjustments, however, did not completely eliminate the significant increase in risk for NICU stay 7 days or longer (OR = 1.2; 95% CI 1.0-1.5) and the neonatal mortality risk even increased (OR 1.8; 95% CI 1.0-3.3), when associated with gestational hypertension (Table III).

Do preeclampsia and unexplained IUGR share similar risk factors?

Mothers with preeclampsia were more likely to have a history of diabetes, renal or cardiac disease, chronic hypertension, previous preeclampsia, BMI >30 kg/cm^2, urinary tract infection and extremes of maternal age than those with IUGR. Conversely, "unexplained IUGR" was associated with higher rates of low birth weight in previous pregnancies. Primiparity and multiple pregnancies were risk factors shared by both conditions. SES was similar in the 3 groups (Table IV).

Table I Risk factors for preeclampsia and gestational hypertension compared with the reference group

	Preeclampsia (n = 874)			Gestational hypertension (n = 2,748)			Reference (n = 31,273)
Risk factors	%	OR*	95% CI	%	OR*	95% CI	%
Diabetes/renal/cardiac disease	2.8	2.4	(1.5-3.6)	3.5	2.7	(2.1-3.5)	1.1
Hemorrhage in 1st or 2nd trimester	2.2	1.0	(0.6-1.5)	3.2	1.4	(1.1-1.7)	2.3
Chronic respiratory conditions	0.7	2.7	(1.2-6.5)	0.3	0.9	(0.4-2.1)	0.2
Preeclampsia in last pregnancy	11.2	12.7	(10.0-16.2)	8.9	9.4	(7.8-11.2)	0.9
Obesity (BMI >30 kg/m^2)	27.1	2.8	(2.4-3.3)	27.4	2.8	(2.5-3.0)	11.9
Low birth weight in last pregnancy	4.0	1.3	(0.9-1.9)	3.8	1.4	(1.1-1.7)	3.1
Previous high-weight infants	1.5	0.9	(0.5-1.7)	3.0	1.7	(1.3-2.2)	1.4
Spontaneous abortions (>2)	3.0	1.0	(0.7-1.5)	3.6	1.0	(0.8-1.3)	3.2
Urinary tract Infection	12.4	1.4	(1.1-1.7)	12.6	1.3	(1.2-1.5)	9.4
Reproductive tract surgery	2.9	1.0	(0.7-1.5)	6.2	2.2	(1.8-2.6)	1.9
Reproductive tract infection	13.5	0.8	(0.6-0.9)	21.1	1.3	(1.2-1.5)	16.1
Maternal age (<16 y)	6.0	1.4	(1.0-1.9)	3.9	1.3	(1.1-1.6)	2.9
Maternal age (>40 y)	2.1	2.8	(1.7-4.5)	2.8	3.0	(2.4-3.9)	1.0
Primiparous	51.4	2.2	(1.9-2.5)	36.3	1.2	(1.1-1.3)	32.4
Smoking†	7.8	0.8	(0.6-1.0)	10.3	1.1	(0.9-1.2)	9.6
Twins	1.5	2.0	(1.2-3.6)	1.2	1.6	(1.1-2.4)	0.7
Socioeconomic status (low)	59.4	1.0	(0.8-1.1)	55.5	0.8	(0.7-0.8)	61.9

* ORs adjusted for all the other variables in the subgroup (variables within horizontal lines) using logistic regression models.
† Smoking adjusted for hemorrhage in 1st or 2nd trimester, respiratory infection, previous high-weight infants, reproductive tract surgery, reproductive tract infection, primiparity, and socioeconomic status.

Table II Gestational age and birth weight according to study subgroups

	Gestational age (wks)			Birth weight (g)		
	n	Mean	SD	n	Mean	SD
Preeclampsia	873	37.5*	2.9	873	2,845*	788
Gestational hypertension	2,743	38.7*	2.1	2,743	3,208*	605
Unexplained IUGR	3,224	39.4*	1.9	3,224	2,555*	358
Reference group	30,927	38.9	2.2	30,985	3,264	507

For definition of study subgroups see Figure. Differences in sample size with those in the Figure are due to missing values for gestational age or birth weight.
* Gestational age and birth weight significantly different from the values for the reference group ($P < .01$).

We further explored the relationship between preeclampsia and "severe unexplained IUGR" (defined as birth weight <5th percentile for gestational age) in relation to the same risk factors as in Table IV. There were 1381 newborn infants in this subgroup, with lower mean birth weight (2402 g, SD 346), but similar mean gestational age (39.6 weeks, SD 1.9) than the overall group. Risk factors were similarly distributed as in Table IV with only wider confidence intervals. These results are not included here but are available on request and in the online version.

Do pregnancies complicated by preeclampsia or unexplained IUGR have similar perinatal outcomes?

As expected by group's definitions, the mean birth weight among IUGR newborn infants was lower (2556 g) than that of the preeclamptic group (2845 g). However, gestational age was lower in the preeclamptic group, 37.5 weeks than the IUGR group 39.4 weeks (Table II). Both unexplained IUGR (OR = 1.8; 95% CI 1.3-2.4) and preeclampsia (OR = 2.5; 95% CI 1.6-4.0) groups were associated with a higher crude and adjusted risk of fetal death than the reference group (Table V).

IUGR group had a lower rate of preterm delivery (5.8%) than the preeclampsia group (27.4%), and that of the reference group (8.8%) (OR = 3.8; 95% CI 3.2-4.4 for preeclampsia and OR = 0.7; 95% CI 0.6-0.8 for IUGR). The rate of very early preterm delivery (<32 weeks) was 4.8% among women with preeclampsia, much higher than those other 2 groups. Of preterm deliveries in the preeclampsia group, 74% were medically indicated; conversely, 59% of preterm in the IUGR group and 71% of those in the reference group followed the spontaneous onset of preterm labor (data not shown in the table).

Table III Perinatal outcomes for preeclampsia and gestational hypertension compared with the reference group

Outcome		Preeclampsia	Gestational HTA	Reference group
Fetal death	n/N (%)	19/874 (2.2)	37/2,745 (1.4)	288/31,183 (0.9)
	Crude OR	2.4 (1.5-3.8)	1.5 (1.0-2.1)	1.0
	Adjusted OR*	2.5 (1.6-4.1)	1.6 (1.1-2.3)	1.0
Preterm delivery (<37 wks)	n/N (%)	239/873 (27.4)	301/2,743 (11.0)	2,718/30,927 (8.8)
	Crude OR	3.9 (3.4-4.6)	1.3 (1.1-1.5)	1.0
	Adjusted OR*	3.8 (3.3-4.5)	1.2 (1.1-1.4)	1.0
Very early preterm delivery (<32 wk)	n/N (%)	42/873 (4.8)	29/2,743 (1.1)	499/30,927 (1.6)
	Crude OR	3.1 (2.2-4.3)	0.7 (0.5-1.0)	1.0
	Adjusted OR*	3.0 (2.2-4.2)	0.6 (0.4-0.9)	1.0
NICU stay 7 or more days	n/N (%)	148/851 (17.4)	181/2,703 (6.7)	1,042/30,849 (3.4)
	Crude OR	6.0 (5.0-7.3)	2.1 (1.7-2.4)	1.0
	Adjusted OR†	1.5 (1.2-2.0)	1.2 (1.0-1.5)	1.0
Neonatal death	n/N (%)	20/852 (2.4)	20/2,696 (0.7)	159/30,793 (0.5)
	Crude OR	4.6 (2.9-7.4)	1.4 (0.9-2.3)	1.0
	Adjusted OR‡	0.9 (0.5-1.8)	1.8 (1.0-3.3)	1.0

* Adjusted for site, treatment group of the original trial and socioeconomic status.
† Adjusted for site, treatment group of the original trial, socioeconomic status, and birth weight (linear).
‡ Adjusted for site, treatment group of the original trial, socioeconomic status, and birth weight (restricted cubic splines with 3 knots).

Table IV Risk factors for preeclampsia and unexplained IUGR compared with the reference group

	Preeclampsia (n = 874)			Unexplained IUGR (n = 3,224)			Reference (n = 31,273)
Risk factors	%	OR*	95% CI	%	OR*	95% CI	%
Diabetes/renal/cardiac disease	2.8	2.2	1.4-3.5	0.7	0.7	0.4-1.0	1.1
Hemorrhage in 1st or 2nd trimester	2.2	1.0	0.7-1.7	2.0	0.9	0.7-1.2	2.3
Chronic respiratory conditions	0.7	1.9	0.7-5.1	0.5	2.3	1.3-3.9	0.2
Chronic hypertension	2.1	19.8	10.1-38.9	0.1	1.2	0.4-3.9	0.1
Preeclampsia in last pregnancy	11.2	12.8	10.0-16.4	1.1	1.2	0.9-1.7	0.9
Obesity (BMI >30)	27.1	2.8	2.4-3.3	8.2	0.7	0.6-0.8	11.9
Low birth weight in last pregnancy	4.0	1.3	0.9-1.9	4.6	1.5	1.2-1.8	3.1
Previous high-weight infants	1.5	0.9	0.5-1.7	0.5	0.4	0.2-0.7	1.4
Spontaneous abortions (>2)	3.0	1.0	0.7-1.5	2.6	0.9	0.7-1.1	3.2
Urinary tract infection	12.4	1.4	1.1-1.7	8.2	0.9	0.8-1.0	9.4
Reproductive tract surgery	2.9	1.0	0.7-1.5	1.9	0.7	0.5-0.9	2.9
Reproductive tract infection	13.5	0.8	0.6-0.9	13.3	0.8	0.7-0.9	16.1
Maternal age (<16 y)	6.0	1.4	1.0-1.9	2.8	0.7	0.6-0.9	2.9
Maternal age (>40 y)	2.1	2.7	1.7-4.5	1.1	1.2	0.8-1.7	1.0
Primiparous	51.4	2.2	1.9-2.5	43.1	1.7	1.5-1.8	32.4
Twins	1.5	2.0	(1.2-3.6)	2.33	3.2	(2.5-4.2)	0.7
Low socioeconomic status	59.4	1.0	0.8-1.1	64.5	1.2	1.1-1.3	61.9

* Odds ratios adjusted for all the other variables in the subgroup (variables within horizontal lines) using logistic regression models.

Newborn infants from preeclamptic pregnancies were at a considerably higher risk of NICU stay 7 days or more, than those from pregnancies with IUGR after adjusting by study site and SES (Table V). These differences are present despite the lower mean birth weight of the IUGR group. Neonatal mortality was increased in both the preeclampsia and IUGR groups, although the preeclampsia group has considerable higher risk in both crude and adjusted analyses (Table V). As expected, outcomes were poorer for the "severe unexplained IUGR" group (birth weight <5th percentile) for fetal death, NICU stay 7 days or longer and neonatal mortality (data not shown, available on request and in the online version).

Finally, we compared the perinatal outcomes among infants with IUGR secondary to preeclampsia (N = 194), IUGR secondary to gestational hypertension (N = 355), and unexplained IUGR (N = 3224). Infants with IUGR secondary to preeclampsia had lower mean birth weight (2164 g) than IUGR secondary to gestational hypertension (2427 g) and the unexplained IUGR (2555 g). Mean gestational age was also lower for

Table V Perinatal outcomes for preeclampsia and unexplained IUGR compared with the reference group

Outcome		Preeclampsia	Unexplained IUGR	Reference group
Fetal death	n/N (%)	19/874 (2.2)	55/3,224 (1.7)	288/31,183 (0.9)
	Crude OR	2.4 (1.5-3.8)	1.9 (1.4-2.5)	1.0
	Adjusted OR*	2.5 (1.6-4.0)	1.8 (1.3-2.4)	1.0
Preterm delivery	n/N (%)	239/873 (27.4)	187/3,224 (5.8)	2,718/30,927 (8.8)
	Crude OR	3.9 (3.4-4.6)	0.6 (0.6-0.8)	1.0
	Adjusted OR†	3.8 (3.2-4.4)	0.7 (0.6-0.8)	1.0
Very early preterm delivery (<32 wks)	n/N (%)	42/873 (4.8)	24/3,224 (0.7)	499/30,927 (1.6)
	Crude OR	3.1 (2.2-4.3)	0.5 (0.3-0.7)	1.0
	Adjusted OR*	3.0 (2.2-4.2)	0.5 (0.3-0.7)	1.0
NICU stay ≥7 days	n/N (%)	148/851 (17.4)	213/3,164 (6.7)	1,042/30,849 (3.4)
	Crude OR	6.0 (5.0-7.3)	2.1 (1.8-2.4)	1.0
	Adjusted OR*	5.2 (4.3-6.3)	2.9 (2.4-3.3)	1.0
Neonatal death	n/N (%)	20/852 (2.4)	26/3,161 (0.8)	159/30,793 (0.5)
	Crude OR	4.6 (2.9-7.4)	1.6 (1.1-2.4)	1.0
	Adjusted OR*	4.1 (2.5-6.6)	1.8 (1.2-2.8)	1.0

* Adjusted for site, treatment group of the original trial and socioeconomic status.
† Adjusted for site and socioeconomic status.

Table VI Perinatal outcomes for IUGR infants secondary to preeclampsia, gestational hypertension, or unexplained IUGR

Outcome		IUGR secondary to preeclampsia	IUGR secondary to gestational hypertension	Unexplained IUGR
NICU stay ≥7 days	n/N (%)	55/184 (29.9)	68/348 (19.5)	213/3164 (6.7)
	Crude OR	5.9 (4.2-8.3)	3.4 (2.5-4.5)	1.0
	Adjusted OR*	4.2 (2.9-6.0)	2.0 (1.5-2.7)	1.0
	Adjusted OR†	1.3 (0.8-2.1)	1.6 (1.1-2.4)	1.0
Neonatal death	n/N (%)	9/185 (4.9)	10/348 (2.9)	26/3161 (0.8)
	Crude OR	6.2 (2.9-13.4)	3.6 (1.7-7.5)	1.0
	Adjusted OR*	4.8 (2.2-10.7)	2.7 (1.3-5.9)	1.0
	Adjusted OR†	1.4 (0.6-3.7)	1.9 (0.7-4.8)	1.0

All denominators include only live birth.
* Adjusted for site, treatment and socioeconomic status.
† Adjusted for site, treatment, socioeconomic status, birth weight and gestational age.

preeclamptic IUGR group (37.5 weeks), than the other 2 groups (38.6 weeks) and (39.4 weeks) for the gestational hypertension IUGR and unexplained IUGR, respectively. Reflecting these values, the incidence of preterm delivery among infants with IUGR secondary to preeclampsia was 28.9%, versus 13.5% among IUGR secondary to gestational hypertension and 5.8% among the unexplained IUGR (data not shown in the table).

We compared for these 3 IUGR subgroups the risk of NICU stay 7 days or longer and neonatal death (Table VI). Because of the differences in birth weight and gestational age described previously, we further adjusted by these 2 variables and presented crude and adjusted ORs in Table VI. IUGRs secondary to preeclampsia had the highest risk for both adverse outcomes after adjusting by study site and SES. These differences were eliminated, however, after adjusting by birth weight and gestational age, suggesting that the excess risks are explained by these mediating variables (Table VI).

Comment

This study examined whether preeclampsia, gestational hypertension, and unexplained IUGR (the latter often assumed to be due to placental insufficiency), could be linked by comparing their risk factors and perinatal consequences in a large recently collected data base from 4 distinct ethnic populations. We found similarities between preeclampsia and gestational hypertension, but our results suggest that unexplained IUGR (eg, those not associated with smoking, undernutrition, secondary to hypertensive conditions, or congenital malformations) is a different entity from preeclampsia. Furthermore, we have confirmed that preeclampsia is a major risk for severe perinatal morbidity and mortality, but that gestational hypertension without proteinuria also independently increases perinatal risk.

Our data are based on a large, prospective study of all women who initiated antenatal care during a fixed period

at clinics serving 4 specific geographic areas. Data were recorded as part of the WHO Antenatal Care Trial, data collection, standardized and monitored specifically for preeclampsia and eclampsia, which were part of the predetermined primary outcomes of the original trial. Ultrasound measures were used to corroborate uncertain gestational age. Clinical management of the primary outcomes followed local standard protocols.

Baseline factors of the original trial were well balanced by intervention groups. There was a marginal difference between the 2 antenatal care models in the incidence of preeclampsia that was not statistically significant. Nevertheless, adjustments were made by treatment arm of the original trial for the outcome analyses.

History of renal disease, diabetes, cardiac disease, and preeclampsia are risk factors for both preeclampsia and gestational hypertension suggesting that the 2 conditions are related to renal pathophysiologic changes and/or vascular anomalies. This underlying renal or vascular disease, as well as being overweight, can predispose for both conditions during future gestations.

However, there are some differences: preeclampsia, but not gestational hypertension, was independently associated with primiparity, as there were chronic respiratory diseases, in agreement with the reported[14] increased risk for preeclampsia among women with asthma. Smoking during pregnancy tends to have a protective effect on preeclampsia,[15] the mechanism of which remains unclear.[16]

Furthermore, there is a suggestion that unlike preeclampsia, gestational hypertension may be associated with reproductive tract infection, hemorrhage during pregnancy, and history of reproductive tract surgery. We did not have detailed information of the timing and treatment provided and severity of these risk factors, which might be markers of some underlying gynecologic condition. For example, there is an association between uterine malformations and unilateral renal agenesis with gestational hypertension and preeclampsia.[17]

Preeclampsia, as it is well known, increases the risk for severe perinatal outcomes, mostly by its effect on reducing birth weight. However, in agreement with other recent multicenter studies of nonproteinuric hypertensive pregnant women,[18,19] gestational hypertension on its own also increased the risk of fetal death, severe neonatal morbidity, and mortality. These results should remind clinicians about the need for a close surveillance of women with gestational hypertension and that even if early delivery is now associated with good outcomes, the increase cost of this strategy cannot be avoided. Unfortunately, detailed long-term consequences of either entity could not be evaluated by us; for example, markers of inflammatory response have been found to be elevated later in life in women who had preeclampsia develop.[20] Such markers could help to differentiate the 2 hypertensive conditions.

We have categorized IUGR after excluding congenital malformations and structural defects, as those related to undernutrition, to smoking, to be secondary to preeclampsia or gestational hypertension and finally, those unexplained IUGR considered as related to placental insufficiency. Placental insufficiency is recognized as the most common cause of fetal growth restriction among clinically healthy, nonsmoking women with adequate nutritional status.[21]

However, we recognize that this classification has limitations. For example, misclassification of newborn infants could have occurred, when we excluded smoker mothers, as this pattern was based only on self-reporting habits or because the definition of nutritional status was based on BMI and severe anaemia only. Furthermore, the "unexplained IUGR group," a broad category might have been differentiated further, if more detailed clinical and/or laboratory information (ie, biologic markers of placental insufficiency) had been sought in the original trial. Had such data been available, we could have excluded more women without evidence of placental compromise from the "unexplained IUGR" group, and excluding these newborn infants would have reduced the contribution of "constitutionally small" infants to the IUGR group. However, while no doubt there are such newborn infants within the "unexplained IUGR" cohort, we believe their proportion to be small. The reason for this view is that, the "unexplained IUGR group" ($<$10th percentile) has considerable higher morbidity and mortality than the reference group, that should not be the case if our IUGR group were diluted with many constitutionally small infants.

Other data support the validity of the "unexplained IUGR" group designation. Two recent publications have challenged the constitutionally small notion in IUGR less than 10th percentile. In 1 from Canada , the increase in the proportion of IUGR less than 10th percentile was associated with higher perinatal mortality, when comparing primiparous with multiparous[22] as it was in the second report comparing black versus white women at all gestational ages.[23] Finally, confining our own analysis to newborn infants less than 5th percentile ("severe unexplained IUGR"), a group, no doubt with less "constitutionally small" newborn infants, produced a distribution of risk factors almost identical to that in the overall "unexplained IUGR" group.

Finally, placental insufficiency could be a pathway, for other conditions affecting the vascular structure of the placenta or reducing blood flow to the fetus, including infections with cytomegalovirus or toxoplasma, which are not always clinically diagnosed during pregnancy.

We noted that diabetes, renal cardiac disease, and chronic hypertension are highly associated with preeclampsia, but are not independent risk factors for unexplained IUGR (Table IV). This may appear to

contradict the literature, but merely reflects the exclusion of IUGR secondary to preeclampsia from the "unexplained" category and suggests that the previously noted medical disorders primarily affect fetal growth by increasing the risk for preeclampsia, and if IUGRs secondary to preeclampsia are removed, the association is no longer present. We did not have accurate information as to when the preeclampsia first presented, a factor that may be different according to the risk factors like diabetes (mostly associated with early-onset preeclampsia). As we have grouped all preeclampsia cases into 1 entity, it may be possible that some subgroups of preeclampsia are associated with unexplained IUGR, while others reflect a different pathophysiology.[24]

IUGR related to placental insufficiency and preeclampsia are suggested to share in some cases placental abnormalities as a common path.[25,26] Interestingly, recent studies have explored a range of markers that could differentiate these 2 conditions. Levels of urinary placental growth (PIGF) factors were shown to be lower about 5 weeks before overt preeclampsia, but such reduction was not observed in women destined to have growth-restricted newborn infants.[27] In another study, circulatory fetal DNA levels were elevated in cases with preeclampsia, but similar in the IUGR and control pregnancies.[28] Finally, women with preeclampsia have different profiles of complement split products than those who deliver SGA neonates.[29] A systematic review of all these evidence is much needed for a complete interpretation of this literature.

In summary, preeclampsia and gestational hypertension seem to be related conditions, both increasing the risk for morbidity and mortality; conversely, preeclampsia and unexplained IUGR appear to be independent entities. Further efforts to characterize them by using biochemical or genetic markers could contribute to their better understanding and, ultimately, their prevention.

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Appendix

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EDITORS' CHOICE

The International Infections in Pregnancy (IIP) study: Variations in the prevalence of bacterial vaginosis and distribution of morphotypes in vaginal smears among pregnant women

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Objective: The objective of the study was to determine the prevalence of bacterial vaginosis and the distribution of associated morphotypes among asymptomatic pregnant women in different countries.

Study design: In 8 institutions participating in the Global Network for Perinatal and Reproductive Health (www.gnprh.org) from July 1999 to September 2001, 1466 women were enrolled. Vaginal smears were Gram stained and scored with Nugent's method at a reference laboratory. The prevalence of bacterial vaginosis and bacterial morphotype distributions were compared.

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Results: Overall, 12.3% of women had bacterial vaginosis according to Nugent's criteria. Zimbabwe had the highest prevalence (24.4%) when compared with all other sites, except Myanmar ($P < .05$). Among bacterial vaginosis cases, 98.9% of vaginal smears had more than 30 *Gardnerella/Bacteroides* morphotypes present per oil immersion field. Individual centers showed significant differences in the number of *Mobiluncus* and lactobacillus morphotypes ($P < .01$).

Conclusion: The prevalence of bacterial vaginosis and distribution of bacterial morphotypes in vaginal smears among asymptomatic pregnant women vary significantly in populations from different countries.

Bacterial vaginosis (BV) is the most common vaginal infection worldwide and is generally asymptomatic. It is prevalent in 11% to 48% of women of reproductive age.[1-5] BV is characterized by an imbalance in the normal vaginal flora in which the normally abundant hydrogen peroxide-producing *lactobacilli* are depleted and anaerobic and microaerophilic organisms like *Gardnerella vaginalis, Mycoplasma hominis, Ureaplasma urealyticum, Mobiluncus, Prevotella,* and *Bacteroides* are markedly increased.[6,7] BV during pregnancy is linked with adverse outcomes such as increased risk of preterm labor, preterm prelabor rupture of membranes, preterm delivery, and possibly spontaneous abortion.[8-10] In addition, many studies have found that BV is associated with chorioamnionitis and postpartum and postabortion endometritis.[10-12] BV may also be associated with an increased risk for human immunodeficiency virus (HIV) transmission between adults as well as perinatal transmission of HIV.[13]

The social, clinical, and economic implications of adverse outcomes associated with BV have led to increased attention to screening and treatment. Studies conducted in the United States have found that there are significant variations in the prevalence of BV among different population subgroups.[14,15] The rate of BV is higher in black women than in any other ethnic group in the United States. Although often of small sample size, there are a number of published international studies investigating the prevalence of BV predominantly in high-risk populations.[2-5,16,17] In a 4-center study conducted in India, Thailand, Malawi, and Zimbabwe, the prevalence of BV was 30%.[17] Other studies conducted in different countries described the prevalence of BV ranging from 11% to 48%.[1-5]

These differences may be explained by the use of different diagnostic criteria. Lately there have been 2 methods used to evaluate BV. One, described by Amsel et al,[18] is a composite method based on clinical and laboratory criteria. The other described by Nugent et al[19,20] has been described as more reliable. In this technique, the diagnosis of BV is based on the interpretation of a Gram stain of vaginal secretions. A score is assigned on the basis of the proportion of lactobacillus morphotypes and *Gardnerella, Bacteroides*, or *Mobiluncus* morphotypes observed under the microscope.[20] A score of 10 is comprised of 4 points for no lactobacillus, 4 points for 4+ *Gardnerella/Bacteroides* (30 or more morphotypes present per oil immersion field), and 2 points for 3+ or 4+ *Mobiluncus* (30 or more morphotypes present per oil immersion field). Of a possible range of 0 to 10, a score of 7 to 10 is considered positive for BV.

A possible cause of variation in reported prevalence might be the manner in which microscopic analysis criteria are applied, from location to location and the interobserver and intraobserver reliability of the methods used.[21] We are not aware of published studies investigating variations in the prevalence of BV among pregnant women from different geographical regions of the world that have used standardized methods for sample collection and interpretation of the Gram-stained samples at a centralized laboratory.

This multicenter, international study used standardized diagnostic methodology to determine the prevalence of BV and distribution of BV-associated morphotypes among asymptomatic pregnant women in different populations in 7 countries.

Material and methods

We conducted a study at 8 institutions participating in the Global Network for Perinatal and Reproductive Health (http://www.gnprh.org). Centers were located in Bogotá, Colombia; Dublin, Ireland; Yangon, Myanmar; Manila, The Philippines; Bangkok and Khon Kaen, Thailand; Philadelphia, PA, in the United States; and Harare, Zimbabwe. The study was approved by the institutional review board at each study center and at the Centers for Disease Control and Prevention of the United States. All institutions were urban academic centers providing obstetric care. To ensure that methods were comparable among sites, we held investigators' meetings, conducted site visits, and reviewed collected data centrally.

We enrolled pregnant women between 18 and 35 weeks of gestation receiving routine antenatal care at the 8 study sites after screening for eligibility from July 1999 to September 2001. Women were excluded from the study if they were in active labor or had symptoms of

Table I Characteristics of study participants overall and by study center

	Colombia	Ireland	Myanmar	Philippines	Bangkok, Thailand	Khon Kaen, Thailand	USA	Zimbabwe	Total
n	155	203	227	202	200	200	69	210	1466
Mean age (range), y	28 (14-43)	28 (16-44)	28 (11-42)	26 (15-43)	26 (16-42)	25 (16-42)	31 (15-46)	23 (12-41)	26 (11-46)
Median years of education (range), years	9 (1-20)	14 (9-19)	7 (0-14)	10 (3-15)	9 (0-16)	9 (4-18)	16 (11-20)	11 (0-13)	10 (0-20)
Smoking, %	6.6	26.6	0.9	1	1.5	0	17.9	0	5.7
Ever douched, %	2.6	1	0	96	2	0	49.3	9.6	17.5
Primigravida, %	28	45	44	39	52	48	18	41	42
Median gestational age (range), week at diagnosis	26 (18-32)	28 (19-32)	25 (18-33)	27 (18-34)	27 (20-32)	23 (18-32)	28 (20-32)	27.5 (18-35)	26 (18-35)

vaginitis such as abnormal vaginal discharge, malodor, burning, or itching. Other exclusion criteria included fever, active vaginal bleeding, use of antibiotics in the 2 weeks before entry into the study, or planned use of antibiotics during the remaining time of the pregnancy. Women with asymptomatic *Trichomonas vaginalis* were not excluded but after sampling received a prescription for therapy for themselves and their sexual partners. Overall, the population at each site was one of convenience with no attempt to select participants based on any specific criteria. The populations in general were mid to low income and reflected the ethnic distribution of the country.

After agreeing to participate in the study, participants signed an informed consent statement. An initial questionnaire was conducted by clinic nurses who had been trained as research assistants. The initial data form included a patient identification number, date of enrollment, gestational age (based on reliable last menstrual period or ultrasound), laboratory test results (including wet mount and other tests as per the clinic routine), demographic data, history of past pregnancies, and any infections diagnosed during this pregnancy. Then a pelvic examination was performed by an obstetrician and samples collected.

Using a Dacron swab, a sample was obtained from the lateral wall of the vagina and smeared onto 2 clean glass slides. One vaginal smear was air dried, Gram stained, scored for BV, and stored at the study center. The second slide was sent for Gram staining and scoring at a reference laboratory at the University of Alabama (UAB) in Birmingham, Alabama, in the United States. BV was ascertained using Nugent scores[20] for Gram stain. All slides were read by the experienced observers at UAB who were blinded to the clinical data. The score from UAB was used for data analysis.

Data were entered using Epi-Info software (Centers for Disease Control and Prevention, Atlanta, GA), and the analysis was conducted using SPSS 12.0 for Windows (SPSS Inc, Chicago, IL). Statistical analysis included χ^2 tests and forward stepwise logistic regression; a P value less than.05 was considered significant.

Results

We enrolled 1466 asymptomatic pregnant women in the study. The median age of participants was 26 years (range 11 to 46 years), with a range of 23 to 31 years among the study centers (Table I). The median gestational age at enrollment was 26 weeks (range 18 to 35 weeks). Smoking was common among women in the United States and Ireland but uncommon elsewhere; douching was common among women enrolled in The Philippines and in the U.S. sites.

Among 1461 vaginal smears available for evaluation, 12.3% (n = 179) were consistent with a diagnosis of BV according to Nugent's criteria. The highest prevalence was in Zimbabwe (24.4%) and the lowest prevalence in Philadelphia, PA (5.8%) (Table II). There were statistically significant differences in prevalence between Zimbabwe and all other sites ($P < .05$). The mean Nugent score was 2.8 ($\pm$2.5) overall and, consistent with the prevalence of BV, was highest in Zimbabwe (4.1). ($\pm$2.7).

By multivariate analysis, the prevalence of BV was associated with women's age, decreasing with each year of age. It was associated with study center but not associated with education level, smoking, or douching (Table III). After accounting for age, education, douching, and smoking, the prevalence of BV in each of the other sites with the exception of Myanmar was significantly less than Zimbabwe with an odds ratio between 0.24 and 0.51.

There were variations in the component scores for lactobacillus, *Gardnerella*/*Bacteroides*, and *Mobiluncus* from the individual centers (Figure 1). The mean scores of all morphotypes were highest for Zimbabwe. Among BV cases (n = 179), nearly all vaginal smears (98.9%) had more than 30 *Gardnerella*/*Bacteroides* morphotypes present per oil immersion field (Figure 2). However,

Table II Prevalence of BV (Nugent score 7 to 10) overall and at individual study sites

Site	n	Prevalence of BV, %	Mean Nugent score (±SD)
Colombia	14/155	9.0	2.6 (2.3)
Ireland	12/201	5.9	2.3 (2.1)
Myanmar	35/225	15.6	2.9 (2.7)
Philippines	15/200	7.5	2.1 (2.2)
Bangkok, Thailand	25/200	12.5	3.0 (2.4)
Khon Kaen, Thailand	23/200	11.5	2.2 (2.3)
United States	4/69	5.8	1.9 (2.0)
Zimbabwe	51/209	24.4	4.1 (2.7)
Total	179/1461	12.3	2.8 (2.5)

individual centers showed significant differences in the number of *Mobiluncus* morphotypes and lactobacillus morphotypes ($P < .01$). None of the samples from subjects with BV in Ireland had *Mobiluncus* morphotypes. In contrast, the prevalence of *Mobiluncus* species at Myanmar, Colombia, Zimbabwe, and the United States was 88.5%, 78.6%, 76.5%, and 75%, respectively. The expected absence of lactobacillus morphotypes was found in only 5.9% of BV cases in Zimbabwe, whereas the proportions in Khon Kaen, Thailand, and Ireland were 43.5% and 41.7%, respectively.

Comment

Our study found important differences in the prevalence of BV among asymptomatic pregnant women from different geographical regions of the world. In addition, we describe significant variation in the distribution of morphotypes in vaginal smears. In Ireland, where the participants were predominantly white, none of the subjects with BV had *Mobiluncus* morphotypes in their vaginal smears, whereas nearly half of the cases had a complete absence of lactobacillus. In Zimbabwe, where all the subjects were black, BV was predominantly the result of a higher proportion of the *Mobiluncus* species, but only 5.9% of women with BV had a complete absence of lactobacillus.

Previously conducted studies in the United States[14,15] also found substantial ethnic differences in the rates of microbial colonization of the vagina. Asian-Pacific Islander and white women had the lowest percentages of positive test results, whereas black women had the highest for nearly every organism studied. Black women were colonized with BV in 23% versus only 9% in white women. After adjustment for potential confounders including certain health behaviors, the odds ratio of a black woman having colonization with BV is 2.9 (95% confidence interval 2.5 to 3.4) when compared with a white woman.

Table III Logistic regression analysis for BV, adjusting for age, education, center, smoking, and vaginal douching

Variables	Odds ratio	95% CI for OR	*P* value
Age	0.95	0.92-0.98	.001
Education	1.00	0.95-1.06	.93
Center			
Zimbabwe	1		
Colombia	0.35	0.18-0.68	.002
Ireland	0.24	0.12-0.48	<.001
Myanmar	0.71	0.43-1.17	.17
Philippines	0.29	0.16-0.55	<.001
Bangkok	0.51	0.30-0.86	.01
Khon Kaen	0.41	0.24-0.72	.002
United States	0.28	0.09-0.81	.02
Smoking			
No	1		
Yes	1.25	0.46-3.44	.66
Douched			
No	1		
Yes	1.75	0.69-4.46	.24

The findings had the potential to explain in part the disparity in pregnancy outcomes, especially rates of spontaneous preterm birth, between black and white women. The prevalence rates we report generally fall within previously reported ranges. Goldenberg et al[14] and Hillier et al[8] reported rates ranging from 9% to 23% and 9% to 28%, respectively, in populations in the United States. Purwar et al[16] reported a rate of 11.5% in India. We confirmed a higher rate in the population from Zimbabwe, as described by other investigators.[2] The low prevalence in the center in the United States in our study (5.8%) could be explained as a result of a small sample size for that center. It could also be explained as a result of a selection bias because these women were from a private practice and were mostly white women. We believe that the rates we report are generally representative of the rate of BV in pregnancy in asymptomatic women from the population at each of the sites.

We used standardized methods for collection of the samples, with dedicated, trained staff and had all the slides stained and read at a central, experienced laboratory. These procedures assure that the explanation for the variation in the prevalence of BV by site is not the result of methodological issues.

Many questions about the association of BV and poor pregnancy outcome remain. Whether these variations in BV prevalence or distribution of morphotypes are related to different outcomes in different populations is unclear. In addition, it is not known which morphotypes of BV, if any, contribute to the adverse outcomes previously associated with BV, such as preterm birth or acquisition of HIV infection. In fact, the mechanisms that trigger

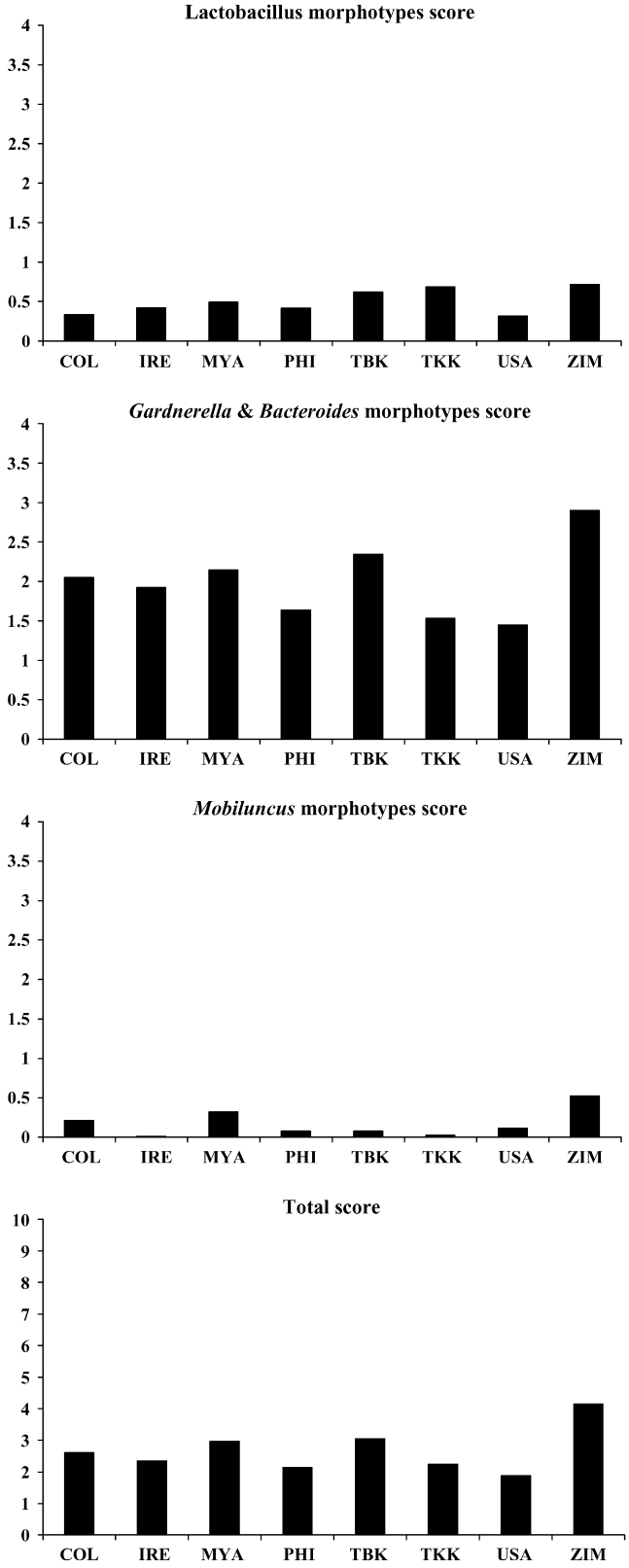

Figure 1 Mean total and component Nugent score for all women evaluated at each study site. *COL,* Colombia; *IRE,* Ireland; *MYA,* Myanmar; *PHI,* The Philippines; *TBK,* Bangkok, Thailand; *TKK,* Khon Kaen, Thailand; *USA,* Philadelphia, USA; *ZIM,* Zimbabwe.

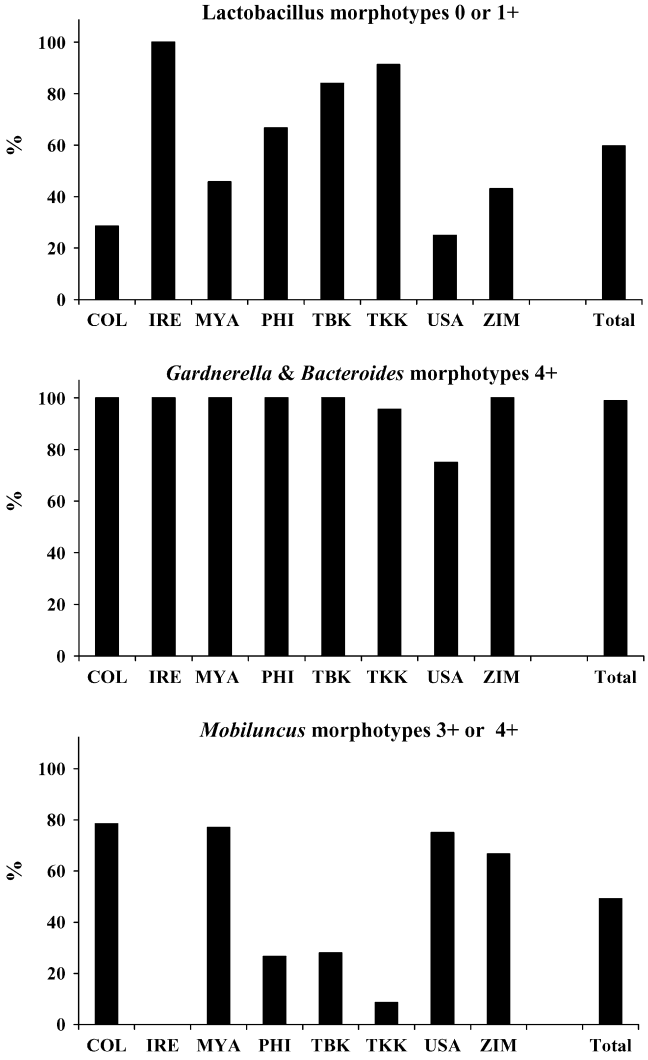

Figure 2 Distributions of morphotypes in BV cases with a Nugent score of 7-10. *COL,* Colombia; *IRE,* Ireland; *MYA,* Myanmar; *PHI,* The Philippines; *TBK,* Bangkok, Thailand; *TKK,* Khon Kaen, Thailand; *USA,* Philadelphia, USA; *ZIM,* Zimbabwe.

change in the vaginal ecology and the roles of the individual microbes causing BV are poorly understood. Other studies have shown increased proinflammatory cytokines, such as tumor necrosis factor-α, interleukin-1, interleukin-6, interleukin-8, granulocyte colony-stimulating factor, fetal fibronectin, and metalloproteinases in conjunction with BV, even though BV is customarily regarded as a noninflammatory condition.[22-26]

The strength of this study was that it is the first multicenter, international study on BV conducted in diverse racial and ethnic populations. Because the methods were standardized across all centers and laboratory tests were done at a central location, the chance of bias resulting from multiple observers reading the slides was eliminated. A limitation was that there was a

small sample from 1 center (the United States), and a single study site may not be representative of the general population in the countries represented.

In conclusion, with Gram stains performed and read in a single reference laboratory, our findings suggest that the prevalence of BV and the distribution of bacterial morphotypes in vaginal smears among asymptomatic pregnant women differ in different countries. Why these differences occur and whether the variation in the distribution of morphotypes associated with BV leads to differences in pregnancy outcomes needs to be further studied.

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Perinatal research in developing countries — Is it possible?

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Summary Maternal mortality remains the health statistic for which there is the greatest disparity between developing and developed countries. The risk of stillbirth or neonatal death is also high in developing countries. The inequality of research funding between rich and poor countries is dramatic, with only 10% of research funding directed towards diseases which contribute 90% of the global burden of disease. The need for high-quality, relevant perinatal research in developing countries is compelling. There are many examples of good perinatal research in developing countries. Nevertheless, significant challenges remain and are being tackled. We need better information about maternal and perinatal health, and about performance of the health services, we need more evaluation of what helps and what harms within the existing health services, and we need improved strategies for implementation of research findings.

Introduction

The inequalities in health between rich and poor countries are well documented. People who live in the rich, developed countries—predominantly in the northern hemisphere—have far healthier and longer lives than those who live in the poor, developing countries, predominantly in the southern hemisphere. These inequalities in health are particularly stark for maternal and child health.

Maternal mortality remains the health statistic for which there is the greatest disparity between developing and developed countries.[1,2] An estimated 529,000 women die each year of pregnancy-related causes.[2] More than 99% of these deaths occur in developing countries, where a woman has an average lifetime risk of dying from pregnancy-related conditions that is about 250 times greater than a woman in most developed countries.[2] Morbidity associated with pregnancy and childbirth is less well documented, particularly

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in developing countries. Nevertheless, the World Health Organization (WHO) estimates that 30 million women develop complications following pregnancy each year. Mortality for children in developing countries is also high, especially at birth and during the first few weeks after birth. Each year 3.3 million babies are stillborn and 4 million die within 28 days of birth.[2]

None of this is new, but it has not always been considered newsworthy. The recent World Health Report[2] outlines how for centuries the care of mothers and young children was regarded as a domestic affair, the realm of mothers and midwives. In the 20th century this purely domestic concern was transformed into a public health priority, first in the rich countries but eventually also in poor countries. This process culminated in the Millennium Development Goals, which included targets for reducing child mortality and maternal mortality as goals 4 and 5.

Research is a vital tool for identifying and tackling health problems. The inequity of research funding between rich and poor countries is dramatic. Only 10% of the US$50–60 billion spent annually on health research worldwide is directed towards diseases which contribute 90% of the global burden of disease.[3,4] Identifying and removing the barriers to research in the developing world is crucial if this balance is to be redressed. Over the next 50 years it is anticipated that 97% of the world's population growth will be in developing countries. If the world is to see the maximum benefit from health research, then the balance of research between the developed and developing countries needs a substantial shift. Worse still is that most of the research conducted in poor countries may be of little, if any, relevance to the people who live there, as it is primarily intended to benefit those who live in rich countries.[3] Such research may be undertaken in the developing world because the disease prevalence is higher (as with AIDS, for example), because ethical constraints are less, or because the cost of doing the research is lower.

If clinicians and policy makers in low- and middle-income countries are to make best use of the health-care resources available to them, they require high-quality relevant evidence to inform their decision-making. They need good research that will improve their understanding of the clinical problems they face and help provide practical solutions. Such research should be conducted in a setting comparable to their existing health services. Once completed, it also has to be published, and then made accessible. There are many barriers to this process in developing countries. These include medical schools and hospitals being in disarray, shortage of money, poor salaries and career structures for academics, lack of local training and mentoring, no local journal for publication, and little guidance on how to write research papers.[5]

The need for perinatal research in developing countries is compelling. Such research needs to address the problems of maternal and neonatal health in a way that is both relevant to the communities and health services of these countries and scientifically robust. We believe such research is possible; much has already been achieved, but much more is still needed. In this chapter we will discuss some of the issues facing perinatal researchers in developing countries, present a range of examples that demonstrate what has been achieved to date, and discuss some of the challenges for the future.

Describing maternal and neonatal morbidity and mortality in developing countries

Reliable data on morbidity and mortality are often taken for granted in developed countries, yet in many developing countries such information is scant, at best. This lack of information may obscure huge health problems and hamper their being tackled. For example, births and deaths are not routinely registered in many developing countries. Cause of death is recorded in only 100 countries of the world, covering one-third of the world's population. Our understanding of what is happening elsewhere has been enhanced by developing appropriate survey methods, often using indirect methods, and statistical modelling techniques. For 62 developing countries, representing 27% of the world's births, the only estimates of maternal mortality are based on statistical modelling.[2]

For many developing countries, the lack of up-to-date, reliable information for planning and evaluation of maternal and neonatal health-care is among the major challenges faced by programme managers, health practitioners and health policy-makers. This lack of information is also a major handicap in the conduct of relevant research and the implementation of evidence-based decision-making. The gap between evidence of effectiveness and clinical practice is well known. Often routine care is not evidence-based, and the elimination of harmful or useless procedures faces strong resistance.[6] Efforts to improve health practice are restricted by lack of data or poor-quality data. Reliable information is needed to estimate the burden of disease or ill-health, to help guide resource allocation and service planning, and to support health policy planning, implementation and evaluation. Improved understanding in all these areas will also facilitate the design and conduct of research relevant to the needs of developing countries.

The WHO Global Data System for monitoring maternal and perinatal outcome is one strategy for overcoming some of these barriers. This began with systematic reviews summarizing the available data on the effectiveness of interventions in the perinatal period in developing countries, and on the incidence and prevalence of maternal ill health.[6,7] A simple data collection system was then developed with the aim of providing locally relevant data to maternal and neonatal health programmes and institutions. This system builds on existing information about maternal and perinatal outcome, and about the functioning and provision of care. The aim is to provide information that will help to improve decision-making and facilitate best practice. This Global Data System utilizes a network of institutions to conduct a series of simple short surveys on specific topics of global relevance. Surveys take place about every 2 years, and each is conducted within a randomly selected sample of the network (cluster survey).

The first survey was conducted in 2004, and focused on assessing the relationship between mode of delivery and maternal and perinatal outcomes among women giving birth in health facilities. It included all women delivering at selected health facilities in Africa and America during

a 3-month period. Health facilities were selected using a stratified multistage cluster sampling design. In the first stage, 129 health facilities delivering 80,218 women and 81,680 newborns were randomly selected from seven countries in Africa, and 120 health facilities delivering 97,095 women and 98,072 newborns were selected from eight countries in America. The cluster unit for the survey was taken from this sample by selecting institutions providing intrapartum care, based on geographic area and whether a private or public facility. The proportion of non-institutional deliveries was estimated for countries or regions where this is relevant. Overall coordination is from WHO in Geneva, with each region having a coordinating centre. Before implementing the survey, staff at each site were trained in data collection, and regional centres were trained in data cleaning and data management.

This survey described the relationship between caesarean section, particularly among women at relatively low risk, and pregnancy outcome in different health-care settings. High levels of caesarean delivery and the lack of unconfounded data on its effect on maternal and perinatal outcomes, combined with the demand for such information from health-care providers and policy-makers, underscore the importance of the survey. Areas lacking routine data were also identified and addressed. Barriers to effective health practices were highlighted, and operational research to implement them planned accordingly. The Global Data Survey is one example of a systematic approach to monitoring maternal and perinatal health-care, thereby offering the opportunity to improve maternal and infant health, facilitate effective health-care services, and plan locally relevant research. In addition, it provides capacity-building in the conduct of research, and in data collection and management.

The challenges of research in developing countries

Conducting high-quality research anywhere in the world is challenging, but as outlined above the barriers are greatest in the developing world. Many of the problems encountered by researchers in the developing world are similar to—albeit more extreme than—those in the developed world. So, for example, securing funding is an issue for all research, but is a far greater barrier in poor countries than rich ones. Long-term follow-up is never easy, but is particularly difficult in poor countries where the population may be mobile, literacy is low and there are no routine systems for recording births and deaths.[8] Other problems are specific to developing countries: for example, deciding whether it is appropriate to use a placebo, or no treatment, for the control group of a randomized trial in situations where active treatment is known to be effective, but is not available locally and is unlikely to be so outside of the research project.[9,10]

For the topic addressed within a trial to be relevant to the community within which it is being conducted, it should, as far as possible, be integrated into the existing health services.[9] Training local health-service staff in how to administer or monitor an intervention is generally preferable to employing or importing new study staff who will leave once the project is over, for example. The use of a pragmatic study design—based on simple, locally relevant procedures, flexible protocols, and minimal data collection—will not only make the study more feasible to conduct; it will mean that the intervention, if proven to be effective, should have fewer barriers to implementation.

Despite the difficulties, there is evidence of progress. Although few randomized trials are conducted in developing countries, the numbers have increased. For example, the number of trials in sub-Saharan Africa rose almost threefold between 1980 and 1999.[11] However, not all of these studies addressed conditions related to the global burden of disease, or the health needs of the local population. Conditions arising during the perinatal period fared particularly poorly. In another survey of trials related to HIV/AIDS in Africa, 15 studies were identified, all from sub-Saharan Africa, which evaluated interventions to prevent mother-to-child transmission (Nandi Siegfried, personal communication). The earliest was published in 1998. Four of these studies were single-centre, six were multicentre within one country, and five were multicentre and multinational. Of these five, one included centres in Europe as well as Africa, whilst the remaining four used only African centres. Overall, 10,448 participants were recruited to these studies, the smallest of which had 75 participants and the largest 1797.

One story—that of calcium supplementation for prevention of pre-eclampsia—demonstrates the potential for perinatal research in developing countries. The suggestion that dietary calcium might explain at least some of the variation in incidence of pre-eclampsia was first put forward in 1962,[12] based on tentative observations of the similarities and differences between pregnant women in Australia and in Ethiopia. An inverse relationship between calcium intake and hypertensive disorders of pregnancy amongst Mayan Indians in Guatemala was described in 1980, when it was proposed that this association might be causal.[13] Initial trials to test this hypothesis were conducted largely in South America and India. Taken together, these studies suggested calcium supplementation reduces the risk of pre-eclampsia by about one-third, but the data were insufficient for firm conclusions about the possible effects on more substantive outcomes such as perinatal death and preterm birth.[14] The recently completed international study recruited 8325 women with a low calcium intake[15] in six developing countries. Results are expected soon.

A subset of the children born to women recruited from private clinics into one trial in Argentina have been traced for 7 years,[16] and 13-year follow-up is under way (Edgardo Abalos, personal communication). Long-term follow-up of children recruited to perinatal trials remains one of the great challenges, although clearly it is possible in at least some middle-income countries.

Asking the right question

Research is about asking questions and then finding and testing answers. If the question is wrong, or unclear, the answer is unlikely to be helpful. To decide whether an intervention does more good than harm, formulating the

question involves deciding who are the people who have the problem, what are the interventions to be compared, and what outcomes need to be measured. In rich countries most pregnant women are healthy and well-nourished. The same is not true in poor countries. So, for example, there is now strong evidence that routine iron supplementation during pregnancy is not worthwhile in Western countries.[17] As all the trials in this systematic review[17] were conducted in developed countries, however, this result cannot easily be applied to the many developing countries in which chronic anaemia is endemic.

HIV/AIDS is a global problem. Although strong and persistent advocacy has given it a high profile in developed countries, over 98% of the global burden of disease is in middle-income and low-income countries.[18] One of the major public health concerns in countries with a high prevalence of the HIV virus is prevention of perinatal transmission. In developed countries a series of trials in the mid-1990s demonstrated that taking antiretroviral drugs during pregnancy and delivery dramatically reduced the risk that infants born to HIV-positive women would have the virus. The problem for developing countries was that these drug protocols were unaffordable. One solution appeared to be using a much shorter, and therefore more affordable, course of an antiretroviral drug, but whilst these trials were still ongoing controversy erupted.[19–21] Whether it is ethical to use a placebo for the control group in a developing country when known effective drugs exist, even though those drugs are not affordable or available, was hotly debated. This issue remains controversial, although some regard it as acceptable to offer the control group the highest standard of care attainable in the country where the study is being conducted.[22]

In many poor countries postpartum haemorrhage remains an important cause of maternal mortality and morbidity. Injectable uterotonics in the third stage of labour offer the best protection against postpartum haemorrhage. However, these are not available in many rural areas of the developed world where women deliver at home, without access to either refrigeration to store the drug safely or to anyone with the training to give injections. In these settings, an oral agent which is stable over a range of temperatures, such as misoprostol, offers considerable potential advantages.[10] If misoprostol does have some protective effect against postpartum haemorrhage, without any unforeseen adverse effects, this could potentially be beneficial. So, whilst a trial comparing oral misprostol with placebo might not be ethical where active management of the third stage is the norm, it may be relevant for some settings in developing countries.[10,23]

A rather different example is the evaluation of routine antenatal care. Antenatal care first evolved around 1910–1915[24] as a response to concern about persistently high levels of maternal mortality in Western countries. A package of antenatal care was outlined in a Ministry of Health document published in the UK in 1929.[24] This document specified the minimum scope and intervals for antenatal care, with a first visit at around 16 weeks followed by 4-weekly visits to 28 weeks, fortnightly to 36 weeks, and weekly thereafter with each visit including abdominal palpation, fetal heart auscultation, urine testing and general health enquiries. No explicit rationale was offered for either the spacing or clinical content of visits. Nevertheless, these guidelines were to establish the basic pattern for antenatal care into the next century.

Only after more than 50 years was there sufficient doubt about the benefits conferred by antenatal care to prompt rigorous evaluation. There have now been several randomized trials evaluating the timing, content, and care-giver for antenatal care.[25] Trials conducted in developing countries have all compared the current standard package of care with a reduced number of visits. By far the largest of these was conducted in 53 hospitals in Argentina, Cuba, Saudi Arabia and Thailand.[26] This large multicentre trial used cluster, rather than individual, randomization. It concluded that the new package of four goal-oriented visits was as good as the traditional multiple visits. The conclusions of a systematic review of all relevant trials were that although providers of antenatal care are unlikely to realize actual cost-savings from a lower number of antenatal visits, women's time and energy, along with staff and buildings, would be freer for other more useful activities.[25]

Innovation and hypothesis generation

Public-sector health professionals working in developing countries are often subjected to enormous clinical workloads. While this is not an ideal situation, it does expose individuals to an exceptionally broad clinical experience, which may lead to identification of disease patterns or the generation of novel therapeutic ideas. One example of this is the independent observation of apparently low rates of pre-eclampsia in Ethiopia and Guatemala, and the suggestion that this might be related to calcium-rich diets in these populations.[12,13] Another is the development of the partogram for monitoring labour progress in midwife-run obstetric units linked to a busy referral unit in Harare, Zimbabwe.[27,28]

Lack of resources may also provide the stimulus for health workers in poor countries to seek new, affordable interventions for common problems. An example is the off-label use of misoprostol for a number of obstetric indications. Health workers from developing countries have been responsible for several innovations, such as the use of misoprostol for labour induction at term,[29] and use of a misoprostol solution to titrate small doses for labour induction.[30] The first randomized trials of misoprostol for the prevention[31] and treatment[32] of postpartum haemorrhage and use of the rectal[33] and sublingual[34] routes of administration were from developing countries.

Protecting participants in research

The ethical issues raised by research collaboration, both within poor countries and between rich and poor countries, are many and complex. Firstly, there is the danger that vulnerable people in poor countries, such as women and children, may be exploited for research which would be difficult to carry out in affluent countries. A series of international agreements on strategies to protect participants in research, dating back to the Nurenberg principles of 1947, have provided guidelines for researchers,[35,36] but adherence to these principles does not necessarily eliminate the

possibility of exploitation. Conversely, there may occasionally be situations in which a local ethics review committee might approve a deviation from this standard in order to address an important health problem in that particular country.[37]

One particularly difficult issue is that of attempting to avoid any activity which may be seen as an inappropriate inducement to women, or their families, to participate in research. For women with very limited access to health-care, participation in a research trial will often mean greatly improved access to health-care in general, and sometimes access to specific treatment (such as surfactant for premature babies) which otherwise would not be available to them. It is almost impossible to avoid some of these realities acting as an inducement. On the other hand, it can be argued that to withhold research from poor communities on the grounds that the access to improved care for participants will act as an inducement would be to deprive them of specific care that would ordinarily not be available to them. However, if such additional care is offered, there should at least be some agreement with the local community about when such provision will be withdrawn once the study ends. This is particularly important for long-term care, for example antiretroviral drugs for women or children who are HIV-positive.

Implementation and changing practice

Effective implementation of evidence-based practice remains a significant challenge.[38] Having access to information alone is unlikely, by itself, to lead to significant improvements in health-care.[38] Active information dissemination and implementation strategies are more likely to achieve change, although the evidence base to support this is not strong.[39]

The WHO Reproductive Health Library (RHL) is an annually updated electronic publication distributed free of charge in developing countries. It includes predominantly Cochrane systematic reviews in reproductive health, together with commentaries written by experts who are familiar with under-resourced settings, short practical guidance documents, and implementation aids (such as educational videos) to facilitate the adoption of evidence-based practices. To try to assess the impact of the RHL, a multicentre cluster randomized trial was conducted in 40 hospitals in Mexico and Thailand.[40] The intervention consisted of three interactive workshops using RHL over a period of 6 months. The focus of the workshops was to provide access to knowledge and enable its use. The main outcome measures were changes in clinical practices, as recommended in RHL, a year after the first workshop.[41] The multifaceted, active strategy to provide health workers with the knowledge and skills to use RHL to improve their practice did lead to increased access to, and use of, RHL. However, no consistent or substantive changes in clinical practice were detected.[42] Access to knowledge is essential but probably not sufficient in itself to lead to change in health-care practices in the short term.

Collaboration and research networks

The perinatal field has many good examples of locally initiated and conducted research, of international trials coordinated within a developing country, and of international trials coordinated from a developed country.

Collaborative networks linking researchers and clinicians in developed and developing countries have the capacity to tackle important issues for maternal and perinatal health in developing countries. Many of these studies also have relevance for the developed world. One example of such a network is that coordinated by the Department of Reproductive Health and Research at WHO. This network has successfully conducted a number of important multicentre randomized trials involving centres in Argentina, China, Cuba, Egypt, India, Mexico, the Philippines, Saudi Arabia, South Africa, Thailand and Viet Nam. These trials have addressed topics as varied as evaluation of a new antenatal care model,[26] misoprostol for the third stage of labour,[43] a programme promoting evidence-based medicine based on the WHO Reproductive Health Library,[40] and calcium supplementation to prevent pre-eclampsia.[15] Ongoing studies coordinated by this network include trials evaluating the effectiveness of alternative nitrofurantoin regimens for asymptomatic bacteriuria during pregnancy, sublingual misoprostol for postpartum haemorrhage, and vitamins E and C for prevention of pre-eclampsia.[44]

Another network has focused on prevention and treatment of eclampsia, and has conducted two major international randomized trials.[45,46] The first[46] was designed to show which of the ways being used to treat women with eclampsia (seizures superimposed on pre-eclampsia) worked best. The background was that an estimated 50,000 women die each year having had an eclamptic convulsion.[47] Although case fatality is high throughout the world, 99% of these deaths involve women in developing countries. For decades, debate had raged about which anticonvulsant was preferable for treatment of eclampsia. Whilst this debate continued, women continued to suffer and die in large numbers, having received interventions introduced on the basis of personal opinion and poorly controlled studies. This study recruited 1687 women at 27 centres in nine developing countries.[46] Magnesium sulphate was clearly more effective than either phenytoin or diazepam.[46] It has been described as the 'most important trial of the twentieth century',[48] and when published the journal editor commented: 'what a triumph for the trialists but a scandal that we had to wait 70 years for the answer'. As noted in the trial report,[46] from magnesium sulphate first being suggested for eclampsia (in 1906) to the introduction of diazepam and phenytoin (in 1968 and 1987, respectively) a possible 42 million women would have had an eclamptic convulsion, and 4 million of them may have died. Unexpected outcomes of this study were that it challenged assumptions about the pathophysiology of eclampsia,[49] and that it changed practice rapidly in developed countries where magnesium was not being used.[50,51]

The next question was whether magnesium sulphate also prevented eclampsia when given to women with severe pre-eclampsia. Again, there was little reliable evidence. The balance of benefit and harm for seizure prophylaxis is quite different from treatment. Most women and their babies do well following pre-eclampsia, and we are not good at predicting who will develop eclampsia. Even if magnesium sulphate reduced the risk of eclampsia, it needed to be very safe to be worthwhile. Although most

maternal deaths are in the developing world, many women in developed countries become severely ill during pregnancy from conditions like pre-eclampsia.[52] Hence this question is directly relevant to developed as well as developing countries. In the second study,[45] 10,141 women participated in a randomized comparison of magnesium sulphate with placebo at 175 centres in 33 countries across four continents; 85% of recruitment was from developing countries. Magnesium sulphate more than halved the risk of eclampsia among women with severe pre-eclampsia, without substantive adverse effects.[45] Centres in 19 countries helped to assess long-term outcome for the children and their mothers.[53] The philosophy that any information about a child is better than none enabled successful tracing of children in settings where follow-up had previously been dismissed as impossible, demonstrating how dedicated and collaborative commitment can achieve high follow-up rates even in the most unpromising circumstances.[8]

Magnesium sulphate is relatively cheap to produce. This research provided strong evidence to support it being made available for prevention and treatment of eclampsia throughout the world.[54]

Facilitating collaboration

Successful collaboration to tackle complex health problems will usually involve working jointly with a range of people from different backgrounds and disciplines. Stimulating and harnessing the collective effort can be both productive and rewarding.[55] The concept of collective ownership is not only that the study is owned by everyone who contributes to it, but also that there is benefit for all. For example, the fact that the Collaborative Eclampsia Trial[46] was launched in Spanish before English probably helped to set the tone for the collaboration that emerged subsequently. Our experience is that important factors in fostering truly collective ownership are: early and widespread consultation on development of the study protocol and trial materials; early and explicit agreement about sharing results with collaborators before submission for publication, authorship and dissemination; face-to-face contact between collaborators, as well as between those responsible for coordination and collaborators; flexibility; being inclusive of everyone contributing, not just senior staff; rapid acknowledgement of all communication from collaborators; and regular and frequent feedback to each centre on their progress and that of the study overall.

Feedback from collaborators in developing countries is that benefits they particularly value include the sharing of knowledge and expertise; enhancing their own capacity to do and to utilize research; appropriate acknowledgement of all contributions; and opportunities to overcome political, cultural and economic barriers to networking and friendship. Another benefit, often difficult to measure, is generating enthusiasm for research particularly in clinical settings, which may be lacking in developing countries. Belonging to an international collaborative group may help motivate people to do their own local research.

Authorship for collaborative research is often published as a collaborative group. Even though each paper lists large numbers of contributors, there remain even more people whose names do not appear but who have, nevertheless, made substantive contributions. For example, junior doctors, midwives and nurses who helped with recruitment and follow-up, and secretarial or administrative staff who facilitated efficient running of the study locally. One strategy to overcome this problem is to give everyone certificates of collaboration.[56] Those with certificates can then add the study to their curriculum vitae, even if they are not listed on the publication.

Conclusions

The need for high-quality, relevant perinatal research in developing countries is compelling. There are many examples of good perinatal research in developing countries. Nevertheless, significant challenges remain, and these are being tackled. We need better information about maternal and perinatal health, and about performance of the health services; we need more evaluation of what helps and harms within the existing health services; and we need improved strategies for implementation of research findings.

Practice points

- Research is a vital tool for identifying and tackling health problems.
- Reliable data on morbidity and mortality are scarce in many developing countries.
- This lack of up-to-date reliable information makes planning and evaluation of maternal and neonatal health-care difficult.
- Access to knowledge is essential, but probably not sufficient in itself to lead to improve health-care.

Research directions

- Of the funds for health research worldwide, 10% is directed towards diseases which contribute 90% of the global burden of disease. Reducing barriers to research in the developing world is crucial if this balance is to be redressed.
- The need for perinatal research in developing countries is compelling. Such research is possible; much has already been achieved, but more is still needed.
- As far as possible, trials should be integrated into the existing health services.
- Researchers need to ask the right questions for developing countries.
- Collaborative networks have the capacity to tackle important issues for maternal and perinatal health in developing countries.

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Cluster randomised trial of an active, multifaceted educational intervention based on the WHO Reproductive Health Library to improve obstetric practices

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Objective We conducted a trial to evaluate the effect of an active, multifaceted educational strategy to promote the use of the WHO Reproductive Health Library (RHL) on obstetric practices.

Design Cluster randomised trial. The trial was assigned the International Standardised Randomised Controlled Trial Number ISRCTN14055385.

Settings Twenty-two hospitals in Mexico City and 18 in the Northeast region of Thailand.

Methods The intervention consisted primarily of three interactive workshops using RHL over a period of 6 months. The focus of the workshops was to provide access to knowledge and enable its use. A computer and support for using both the computer and RHL were provided at each hospital. The control hospitals did not receive any intervention.

Main outcome measures The main outcome measures were changes in ten selected clinical practices as recommended in RHL starting approximately four to six months after the third workshop. Clinical practice data were collected at each hospital from 1000 consecutively delivered women or for a 6-month period whichever was reached sooner.

Results The active, multifaceted educational intervention we employed did not affect the ten targeted practices in a consistent and substantive way. Iron/folate supplementation, uterotonic use after birth and breastfeeding on demand were already frequently practiced, and we were unable to measure external cephalic version. Of the remaining six practices, selective, as opposed to routine episiotomy policy increased in the intervention group (difference in adjusted mean rate = 5.3%; 95% CI –0.1 to 10.7%) in Thailand, and there was a trend towards an increased use of antibiotics at caesarean section in Mexico (difference in adjusted mean rate = 19.0%; 95% CI: –8.0 to 46.0%). There were no differences in the use of labour companionship, magnesium sulphate use for eclampsia, corticosteroids for women delivering before 34 weeks and vacuum extraction. RHL awareness (24.8–65.5% in Mexico and 33.9–83.3% in Thailand) and use (4.8–34.9% in Mexico and 15.5–76.4% in Thailand) increased substantially after the intervention in both countries.

Conclusion The multifaceted, active strategy to provide health workers with the knowledge and skills to use RHL to improve their practice led to increased access to and use of RHL, however, no consistent or substantive changes in clinical practices were detected within 4–6 months after the third workshop.

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The WHO Reproductive Health Library (RHL) is an annually updated electronic publication.[1] It includes predominantly Cochrane systematic reviews in reproductive health together with commentaries written by experts on the topic and familiar with under-resourced settings, short practical guidance documents, and implementation aids (such as educational videos) to facilitate the adoption of evidence-based practices. RHL is published in English and Spanish with new topics

added and updated topics revised on an annual basis. Initiatives such as RHL address some of the limitations in knowledge access and management difficulties faced by reproductive health care professionals in low- and middle-income countries. Despite several recent successful initiatives such as the Health Internetwork project knowledge access problems for health workers in many low- and middle-income countries are far from over. Difficulties with internet access, high costs of mailing and subscriptions are major barriers to knowledge access.[2] These difficulties are greater for health workers outside research settings involved mainly in routine care.

Effective implementation of evidence-based practices remains a significant challenge.[3] Having access to information alone is unlikely by itself to lead to significant improvements in performance.[4] Active information dissemination and implementation strategies are more likely to achieve change, although the evidence base is not conclusive.[3] The objective of this trial was to assess whether an active educational strategy to promote the use of evidence-based practices in RHL would improve hospital obstetric practices. We hypothesised that a series of interactive workshops to provide health care workers access to relevant information, develop skills and knowledge to use systematic reviews would achieve this goal.

Methods

Setting

The trial was conducted in Mexico City municipal area, Mexico, and the Northeast region of Thailand. Maternity units of hospitals with >1000 deliveries per year, not associated directly with a university or other academic/research department, were eligible to participate. Twenty-two of 34 eligible hospitals in Mexico met the requirements and agreed to participate in the trial. In Thailand, 18 of 19 hospitals in the Northeast region agreed to participate in the trial. The study settings and methods were published in detail.[5]

Study design

We used a stratified cluster randomised design, with the hospitals as the units of randomisation.[5] The stratified allocation was based on country, type of hospital and number of births per year (>5000 or 5000 or less) (Figure 1). The random allocation sequence was produced centrally by WHO in Geneva, assigning hospitals at random in each stratum to intervention or control. Country investigators were informed of the allocation status of the hospitals after collection of baseline data was completed and when the first workshop had to be organised as required in the protocol.

Since inferences, and therefore the analysis, are at the hospital or cluster level, sample size calculations are based on the hospital as the unit of analysis.[6] We calculated the power using standard formulae for comparison of proportions in a completely randomised design and estimated that with 40 hospitals, we would have 90% power to detect a decrease or an increase in a practice equal to the SD between hospitals, in a one-sided significance test at 5% level of significance.[5] For example, if the SD of use of episiotomy is 20%, we would be able to detect a decrease in the end-of-study rate of use of episiotomy from 70 to 50%. We used a one-sided significance test because we believed the intervention could only improve the use of evidence-based practices.

We planned to estimate the prevalence of a practice in a hospital based on a minimum of 1000 women (cluster size). This number would provide a maximum error of estimation of 10% using a 95% CI. For example, we estimated that about 10% of all women admitted to labour ward would have preterm babies and thus be eligible for corticosteroid administration. Therefore, we decided to collect data from 1000 consecutive deliveries in each hospital, both at baseline and at end-of-study or, for practical reasons, for 6 months if this time was elapsed before reaching the target.

Intervention

We implemented a multifaceted intervention based on using RHL, which also addressed potential barriers to the implementation of evidence-based practices (Table 1) in the intervention group hospitals. Interactive workshops comprised the central activity of the intervention.

The first workshop focused on giving information about the project, WHO's role, the principles of evidence-based decision-making and presenting RHL. The second workshop focused on RHL contents and the third on how to implement change. The workshop facilitators were instructed to focus on the use of RHL in general rather than on specific clinical interventions. The hospital RHL coordinators were identified at the beginning and were available to assist staff from the first workshop onwards.

The workshops were conducted over a period of 6 months (at time 0, after 6 weeks and after 6 months) between October 2001 and October 2002. We aimed to include all staff (doctors, midwives, interns and students) at all three workshops. The highest attendance was at the first workshops, but the other two workshops were also well attended. It was not possible to measure attendance with high precision due to staff turn over and participation of students and staff from other departments (anaesthetists, neonatologists). The computers remained operational throughout the trial, although in some hospitals they were not accessible after hours.

The control hospitals did not receive any intervention. These hospitals gave consent to participate in the trial and were informed that computers and printers, plus a training workshop would be provided at the end of the trial.

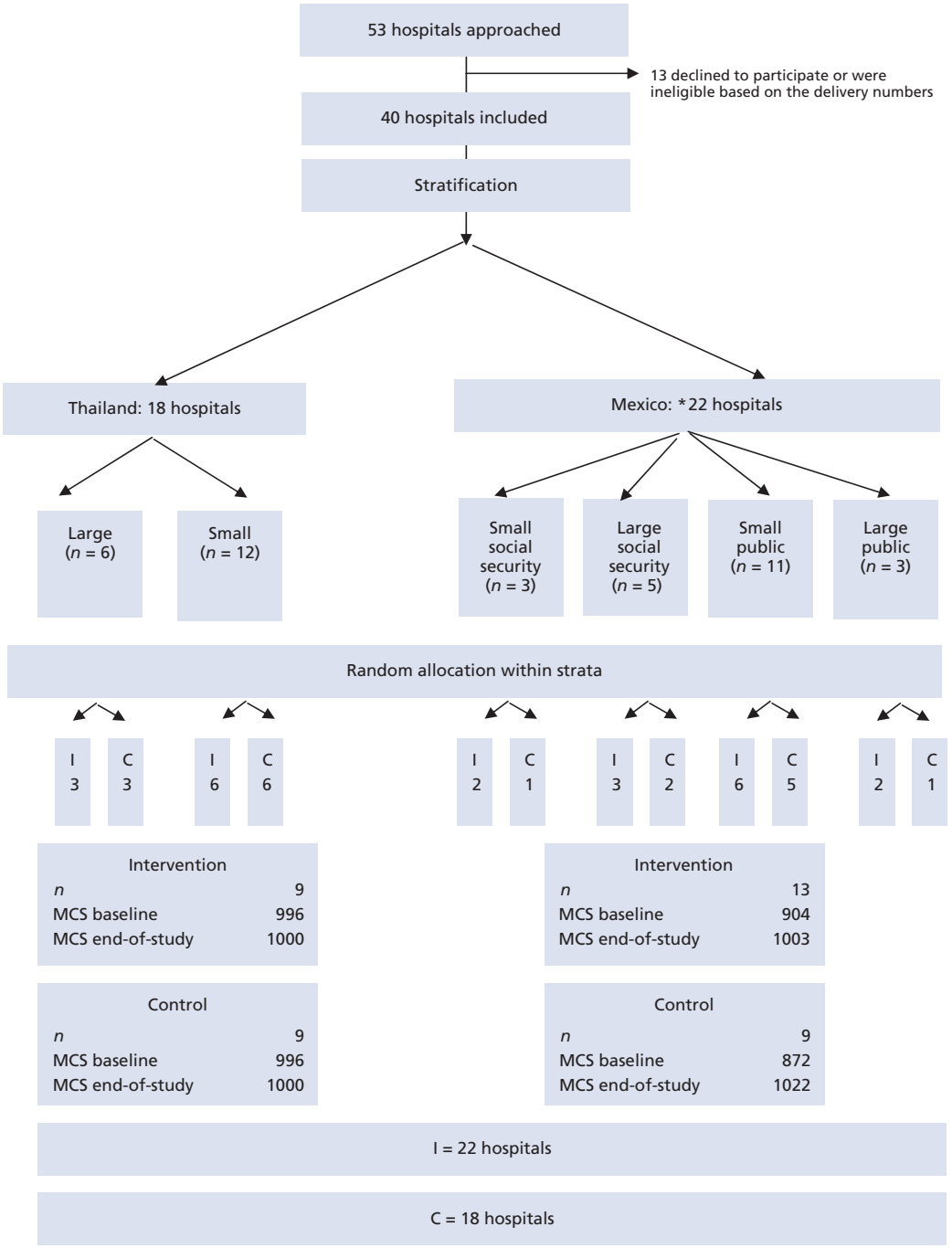

Figure 1. Flow chart of the trial design and random allocation. *In Mexico one hospital classified as large-social security withdrew after random allocation because of building renovation in the maternity. Another hospital that consented to participate that belonged to the small-state stratum was randomised; I, intervention group; C, control group; MCS, mean cluster size (denominators vary depending on the measured practice).

Outcomes and blinding

Main outcomes

The selected practices ranged from relatively straightforward changes such as prescribing antibiotics to women at caesarean section to those that required organisational change within the units (e.g. policy of allowing labour companions). We focused on practices with strong evidence of benefit or harm based on Cochrane reviews and commentaries included in RHL, related to pregnancy and childbirth (intervention site being labour wards), data related to their use could be collected

Table 1. Intervention components

Item	Purpose
Meeting with hospital directors/heads of obstetrics and gynaecology departments	To ensure organisational buy-in
Provision of RHL, computers, printers	To enable access to knowledge
Select hospital RHL coordinator from staff	Assist staff to use RHL and to maintain links with the research team in case of problems
RHL information/advocacy materials (brochures, poster)	To promote awareness among staff
Three interactive workshops by a specialist	To teach principles of evidence-based decision-making, use of RHL and how to use evidence

from routine hospital records, and the issue/problem was believed to be common in both settings (Table 2). We also measured some practices with no clear conclusion as dummy variables (not shown). The hospital staff were unaware of the primary outcome practices. Field workers not involved in the implementation of the trial collected outcome data in the postnatal wards from hospital records, but the mothers could be consulted if information was missing in the records.

We aimed to measure the outcomes 10–12 months from the time of the first workshop (or 4–6 months after the third). We expected that the intervention should begin having an effect from the time of the first workshop onwards at least for some relatively straightforward practices.

Process outcomes

We conducted surveys of medical and nursing staff at baseline and at the end of the study outcome assessment stages to evaluate the knowledge and use of RHL, and other information seeking and utilisation behaviours. The end-of-study survey in Thai control hospitals was conducted at a later stage, and the data were not used due to likelihood of contamination with other evidence-based health care-related activities and low response rate.

Table 2. Practices selected as main outcomes

1	Social support during labour
2	MgSO4 for eclampsia
3	Corticosteroids to women with preterm birth
4	Selective episiotomy
5	Uterotonic use after birth*
6	Breastfeeding on demand*
7	External cephalic version**
8	Iron/folate supplementation*
9	Antibiotic use at caesarean section
10	Vacuum extraction for assisted birth

*Ceiling effect (>70%).
**Unable to measure.

Analysis

A 'hospital' is the unit of analysis. We calculated the change in practice rates before and after the intervention for each hospital. The mean change was calculated and compared between arms for each country separately, using analysis of variance (ANOVA) techniques adjusted for strata. Analysis of covariance was also used, using the baseline rate as covariate to obtain adjusted end-of-study rates.[7] For low event rates, we used nonparametric ANOVA.

Before the analysis, we stated that we would declare the whole intervention effective if statistical significance at the 5% level was shown for the majority of the outcomes.[5] We also stated that we expected that the intervention 'holds at least a clinically relevant numerical edge over the control for those primary endpoints for which demonstration of statistical significance is not achieved'. It is generally accepted that no adjustment for multiple endpoints is necessary under this scenario.[8] We assumed *a priori* that for practices with a frequency of over 70% at baseline, there would be a ceiling effect for practice improvement.

The study was approved by the Scientific and Ethical Review Group of the UNDP/UNFPA/WHO/World Bank Special Programme on Research, Development and Research Training in Human Reproduction, and the participating institutions. Consent to participate was obtained only at the hospital level.[9]

Results

The trial flow chart is presented in Figure 1. The workshops took place between October 2001 and October 2002 in the two countries. In Mexico, obstetric care is provided almost exclusively by doctors in both state and social security hospitals. The median number of doctors per hospital was 20 (range 7–102) in intervention and 14 (8–53) in control hospitals. The median number of deliveries annually was 4382 and 3625 for the intervention and control hospitals, respectively. In Thailand, registered nurses with midwifery training usually provide the routine obstetric care. In Thai

hospitals, the median number of doctors was 6 (range 3–18) and 5 (2–11) in the intervention and control groups respectively, and the number for nurses were 15 (10–28) and 13 (7–20), respectively. The trial workshops were successfully implemented although the implementation of health sector reform initiatives in Thailand resulted in a prolonged interval (up to 6 months in some) interval between the second and third workshops.

We present the results by country with all other strata combined because we did not find any significant difference in outcomes within strata at 5% level.

Main outcomes

Uterotonic use after birth, breastfeeding on demand and iron/folate supplementation were already widely used in both countries (ceiling effect) and will not be evaluated further. In Mexico, the end-of-study rates adjusted for baseline rates and strata were not statistically or clinically significantly different in the intervention and control arms for any of the outcomes studied (Table 3). Similarly, in Thailand, none of the adjusted end-of-study rates in the intervention hospitals were statistically significantly different to those in the control. There was however, a higher reduction in the use of episiotomy in the intervention hospitals which was of borderline statistical significance (Table 4).

Companionship during labour was virtually nonexistent in both countries at baseline. They increased at the end-of-study to more than 50% in three intervention hospitals and in one control hospital in Thailand, while no change in any of the hospitals could be detected in Mexico.

Corticosteroid use for women with extreme preterm babies (gestational age <34 weeks) showed large variation, some hospitals showing large increases and some others large decreases in the use of this practice, in both arms. Changes in Mexico hospitals varied from –42.9 to +92.3% and in Thailand, from –20.3 to +36.0%. Corticosteroid use increased in eight of 13 intervention hospitals in Mexico compared with three of nine control hospitals. In seven of the eight intervention hospitals, the increase in corticosteroid use was more than 10%. In Thailand, four of nine and five of nine hospitals in the intervention and control groups respectively showed an increase in corticosteroid use.

Selective episiotomy was measured by the number of women not having an episiotomy with spontaneous vaginal delivery. Changes in Mexico hospitals varied from –58.2 to +25.6% and in Thailand from –7.3 to +20.9%. In Thailand, six of nine intervention hospitals and one of nine control hospital reduced their episiotomy rates and there was a modest 5.3% (95% CI –0.1–10.7%) difference in reduction of episiotomy in favour of the intervention group.

In Mexico, ten of 13 intervention hospitals showed an increase in antibiotic use at caesarean section compared with five of nine control hospitals. Seven of these ten were more than 10% (range 10.3–74.2%), although in two intervention

Table 3. Effect of the intervention on practices in Mexico (for all outcomes the intended effect of the intervention is an increase in the practice rates expressed in percentage)

Outcomes	Intervention				Control				Difference in adjusted end-of-study rate (I–C)		
	Baseline mean rate (number of women)	End-of-study mean rate (number of women)	Adjusted end-of-study rate*	Rate change**	Baseline mean rate (number of women)	End-of-study mean rate (number of women)	Adjusted end-of-study rate	Rate change	Difference	95% CI	*P* value
Social support during labour	3.5 (11748)	1.0 (13037)	0.7	−2.5	1.2 (7844)	0.2 (9199)	0.7	−1.0	0.1	−0.2 to 0.4	0.58
MgSO4 for eclampsia	5.8 (75)	27.5 (49)	23.5	26.5	10.1 (49)	17.2 (59)	19.6	11.1	3.8	−52.9 to 60.6	0.88
Corticosteroids at <34 weeks	18.9 (248)	26.8 (237)	24.2	7.9	18.2 (371)	22.2 (349)	18.9	4.0	5.3	−18.6 to 29.2	0.64
Selective episiotomy	19.7 (7175)	14.0 (9014)	14.6	−5.7	16.7 (4436)	11.1 (5500)	11.4	−5.6	3.2	−6.5 to 13.0	0.49
Antibiotic use for caesarean section	11.3 (4318)	25.8 (3891)	23.0	14.5	4.1 (3294)	6.5 (3613)	4.0	2.4	19.0	−8.0 to 46.0	0.12
Vacuum extraction delivery	0.6 (11748)	0.2 (13037)	0.2	−0.4	0.4 (7844)	0.1 (9199)	0.1	−0.3	0.1	−0.1 to 0.2	0.37

*Adjusted by baseline rates.
**Rate change, end of study—baseline mean rate including hospitals that have cases for the condition.

Table 4. Effect of the intervention on practices in Thailand (for all outcomes the intended effect of the intervention is an increase in the practice rates expressed in percentage)

Outcomes	Intervention				Control				Difference in adjusted end-of-study rate (I–C)		
	Baseline mean rate (number of women)	End-of-study mean rate (number of women)	Adjusted end-of-study rate*	Rate change**	Baseline mean rate (number of women)	End-of-study mean rate (number of women)	Adjusted end-of-study rate	Rate change	Difference	95% CI	*P* value
Social support during labour	1.3 (8961)	19.7 (8998)	19.7	18.4	0.8 (8964)	6.7 (9000)	1.5	5.9	18.2	−7.2 to 43.6	0.15
MgSO4 for eclampsia	81.9 (20)	57.9 (29)	66.0	−26.5	56.7 (38)	72.6 (35)	77.2	17.1	−11.2	−55.2 to 32.8	0.58
Corticosteroids at <34 weeks	22.8 (191)	27.2 (262)	24.2	4.4	13.0 (214)	19.5 (268)	20.4	6.5	3.8	−12.7 to 20.4	0.63
Selective episiotomy	12.0 (5874)	16.2 (5514)	16.1	4.2	12.1 (6029)	10.9 (5314)	10.8	−1.2	5.3	−0.1 to 10.7	0.05
Antibiotic use for caesarean section	40.1 (2326)	26.0 (67)	23.5	9.8	6.4 (113)	14.7 (69)	32.5	13.9	4.6	−17.7 to 26.9	0.66
Vacuum extraction delivery	7.5 (8691)	7.6 (8998)	7.7	0.1	6.3 (8964)	6.7 (9000)	7.7	0.4	0.0	−1.5 to 1.4	0.95

*Adjusted by baseline rates.
**Rate change, end of study—baseline mean rate including hospitals that have cases for the condition.

hospitals antibiotic use decreased by more than 37%. There were also increases in the five control hospitals that ranged between 2.9 and 10.3%. In Thailand, six of nine hospitals in both the intervention and control groups increased their antibiotic use at caesarean section. The increases ranged between 0.2 and 87.7% and 0.9 and 69.7% in the intervention and control group hospitals, respectively. The baseline antibiotic use for caesarean section varied from 0 to 57.1% in Mexico and from 0 to 96.9% in Thailand, indicating high levels of baseline variation across hospitals.

Process outcomes

In Mexico, knowledge of RHL increased from 24.8 (78/314) to 65.5% (210/307) and 33.5 (65/194) to 39.2% (62/158) in the intervention and control groups, respectively. The proportion of staff using RHL once a month increased from 4.8 to 34.9% in the intervention and from 7.2 to 12.7% in the control group. In Thailand, knowledge of RHL was 33.9 (57/168) and 38.2% (58/152) in the intervention and control groups at baseline. In the intervention group, knowledge of RHL increased to 83.3% (120/144). RHL use increased from 15.5 to 76.4% in the intervention hospitals.

Discussion

We conducted a rigorous evaluation of a strategy to improve health care practices that consisted of providing access to Cochrane reviews and commentaries with an active educational and interactive programme. This multifaceted strategy did not affect the targeted practices in a consistent, predictable and substantive way. Awareness about RHL and its use increased considerably in the intervention groups in both countries.

The evaluation design, i.e. a cluster randomised controlled trial, is one of the major strengths of this trial. The rate changes recorded in the intervention hospitals could have led to biased (over) interpretation of the effects if we had not had a control group. Another strength was the intervention: compared with similar previous work in this area,[10] ours was more intensive and took into account evidence from systematic reviews that suggest that interactive educational interventions are more likely to be effective than didactic sessions. However, it must be emphasised that the evidence base in favour of interactive workshops is indirect (based on comparisons of each to no intervention) and its generalisability to different settings and contexts could be limited.[11]

Thirdly, another strength of the study was that we measured actual practices rather than relying only on knowledge change and reports of practice by clinicians. The latter point has been a common problem in the evaluation of educational interventions in the past. The following examples illustrate the importance of this approach. At one of the Mexican hospitals, the workshop participants claimed that antibiotic use

at caesarean section was routine at that hospital. The actual data showed 0.7 and 0.5% antibiotic use at caesarean section in this hospital at baseline and end-of-study. We were surprised with the low use of magnesium sulphate because we expected that both in Mexico and Thailand there would be a ceiling effect for this practice. In fact, in Mexico, more women received phenytoin as the anticonvulsant.

In spite of these strengths, we did not achieve consistent, statistically and clinically significant effects. A number of circumstances may have contributed to the limited and inconsistent results. Contamination between groups may have resulted from other introduction efforts on evidence-based medicine and the RHL that were taking place separately from our intervention ('background noise'). In Mexico, doctors' dual appointments, i.e. some doctors working in both public and social security hospitals, may have also contributed to contamination.

Our focus on 'knowledge access', instead of targeting one or two interventions, may have decreased the chances of a positive effect on specific practices. Indeed, we did not inform the staff of the practices we selected as outcomes, but rather focused on giving them the knowledge and skills to use RHL, extract the information that they would identify as important and implement the change. This approach may have been insufficient to produce an effect within the timeframe of this trial. However, most behaviour-change interventions aim to achieve a demonstrable effect around 1 year and some even at shorter time points.[12] We believe it was reasonable to expect change in some practices in 1 year. Without any active intervention, it would take longer to achieve behaviour change. A retrospective analysis of obstetric practices in the UK showed substantial shifts over a period of 8 years, although it is not clear when the change took place.[13]

There were various barriers, including language in Thailand, that may have contributed to the lack of effect, some of them beyond hospital clinical staff's control[14]. Since our intervention targeted primarily clinical staff, some institutional and other organisational barriers, whether perceived or real, may have impeded change. Unfortunately, formal barrier assessment before the intervention and tailoring the intervention accordingly does not guarantee effective implementation either.[15]

Another possible explanation to the lack of effect is the way recommendations are made in RHL. Since RHL does not include 'cook-book style' guidance algorithms, it may not have been easy for physicians and nurses to translate the messages in Cochrane reviews and commentaries into concrete changes in practice.

Although the overall results are negative with regard to the primary trial hypothesis, the intervention did seem to influence staff behaviour for some outcomes. The increase in antibiotic use at caesarean section in Mexico and modest reduction in the use of episiotomy in Thailand suggest that the intervention may have had an influence on those practices. The outcomes requiring more complex interactions and structural changes could be more difficult to change and require a longer period of time, for example, companionship during labour or magnesium sulphate for pre-eclampsia/eclampsia.[16,17]

Knowledge access has been suggested as potentially the single most cost-effective and achievable strategy for improvement in health care.[18] However, the multifaceted, active strategy to provide doctors and nurses with the knowledge and skills to improve their practice described here did not lead to consistent or substantive changes although knowledge and use of RHL increased considerably. Knowledge access is essential but probably not sufficient to lead to change in health care practices within a period of 10–12 months.

Conflict of interest

A.M.G., J.V., P.L. and A.L. are editors of The WHO Reproductive Health Library since its inception in 1997 to date.

Contribution to authorship

All authors are members of the Steering Committee of the trial and participated in the conceptualisation and implementation of the trial. All authors read, commented and approved the manuscript. A.M.G. is the guarantor of the manuscript.

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Optimising reproductive and child health outcomes by building evidence-based research and practice in South East Asia (SEA-ORCHID): study protocol

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Abstract

Background

Disorders related to pregnancy and childbirth are a major health issue in South East Asia. They represent one of the biggest health risk differentials between the developed and developing world. Our broad research question is: Can the health of mothers and babies in Thailand, Indonesia, the Philippines and Malaysia be improved by increasing the local capacity for the synthesis of research, implementation of effective interventions, and identification of gaps in knowledge needing further research?

Methods/Design

The project is a before-after study which planned to benefit from and extend existing regional and international networks. Over five years the project was designed to comprise five phases; pre-study, pre-intervention, intervention, outcome assessment and reporting/dissemination. The study was proposed to be conducted across seven project nodes: four in South East Asia and three in Australia. Each South East Asian study node was planned to be established within an existing department of obstetrics and gynaecology or neonatology and was intended to form the project coordinating centre and focus for evidence-based practice activities within that region. Nine hospitals in South East Asia planned to participate, representing a range of clinical settings. The three project nodes in Australia were intended to provide project support.

The intervention was planned to consist of capacity-strengthening activities targeted at three groups: generators of evidence, users of evidence and teachers of evidence. The primary outcome was established as changes in adherence to recommended

clinical practices from baseline to completion of the project and impact on health outcomes.

Discussion

The SEA-ORCHID project was intended to improve care during pregnancy and the perinatal period of mothers and their babies in South East Asia. The possible benefits extend beyond this however, as at the end of this project there is hoped to be an existing network of South East Asian researchers and health care providers with the capacity to generalise this model to other health priority areas. It is anticipated that this project facilitate ongoing development of evidence-based practice and policy in South East Asia through attracting long-term funding, expansion into other hospitals and community-based care and the establishment of nodes in other countries.

Background

Importance of the health problem

Each year there are over half a million maternal deaths worldwide and 98 percent of these occur in the developing world. This represents a tragic and striking health risk differential between the developed and developing world. For women in Asia the lifetime risk of maternal death is one in 65 compared with one in 1,800 for women in developed countries [1].

The main causes of mortality directly related to pregnancy and childbirth are unsafe abortions, bleeding, infection, hypertension (including eclampsia) and obstructed labour [2]. The majority of maternal deaths occur after the birth but many are related to conditions that present earlier in pregnancy. Serious acute and chronic maternal morbidity has been estimated to occur in one in four women [3].

Perinatal and early infant deaths are also high in developing countries. Each year there are almost eight million stillbirths and early neonatal deaths. These arise because of poor maternal health and pregnancy care. Associated morbidity manifests as low birth weight, asphyxia and infection [4].

The high rate of maternal, infant and child mortality in SE Asian countries has been associated with poverty, reduced education and literacy, lack of remunerative employment, low social status, and limited access to health services and family planning [5]. SE Asia accounts for one quarter of the world's population and more than half of the worlds poor. Solutions to these problems require an inter-sectoral approach. This has been supported by many international bodies such as the World Health Organization, World Bank, United Nations Children’s Fund and United Nations Population Fund.

Access to scientifically valid and up-to-date information is a prerequisite for allocation of resources according to evidence and need. Most health workers and policy-makers in developing countries do not have easy access to the latest reliable information on effective care or may not have the skills to evaluate and implement such evidence [6].

A variety of problems arise when clinical practices that are not based on sound scientific evidence are incorporated into established healthcare practice. Valuable resources continue to be used in some developing countries to fund practices of unknown effectiveness, for example electronic fetal monitoring during labour [7]. On the other hand, interventions that have been shown to be both cheap and effective, such as magnesium sulphate to prevent and treat eclampsia, have not been widely implemented [8]. In an empirical example of clinical practice being at odds with published recommendations, a study conducted in six centres in SE Asia and two in the United States of America, demonstrated a large variation in the use of antibiotic prophylaxis in caesarean section, despite there being strong evidence supporting its use [9]. Only two of the eight participating centres routinely administered appropriate regimens of antibiotics at the appropriate time.

Clearly a mechanism is needed to provide healthcare practitioners in the developing world with access to relevant evidence, a means of determining their own evidence requirements and the infrastructure to disseminate and implement clinical practice change based on that evidence. The effects of this provision then need to be evaluated to inform future initiatives aiming to improve health care.

Previous work instigating this project

The Cochrane Collaboration is an international organisation of healthcare practitioners, researchers and consumers that prepares and disseminates systematic reviews of high quality evidence about the effects of healthcare interventions [10]. The growth of the Cochrane Collaboration is well known, with over 3000 reviews published since 1995 and an estimated 11,500 contributors worldwide.

However, this growth has been predominantly in the developed world, and a key objective of the Cochrane Collaboration is to ensure growth of this research activity in the developing world. The Cochrane Developing Countries Network has been established to pursue strategies for encouraging the involvement of contributors from low- and middle-income countries, both in producing reviews and in implementing their findings. In 2004, the level of developing country involvement in the Cochrane Pregnancy and Childbirth Group was modest, with 59 review authors from 11 developing countries and only eight review authors from SE Asia. In the Cochrane Neonatal Group there were 11 review authors from seven developing countries and only three of these were from SE Asia.

In a joint project between WHO, UNDP/UNFPA/WHO/World Bank Special Programme of Research Development and Research Training in Human Reproduction (HRP), South African Cochrane Centre and WHO Regional Office for Africa, the *WHO Reproductive Health Library* [11] derived in part from reviews in *The Cochrane Library*, was made available and practitioners trained in its use within South Africa [12]. Introducing a similar initiative in SE Asia, along with increasing the capacity for involvement in the Cochrane Collaboration and use of *The Cochrane Library*, has the potential to contribute to addressing the issues surrounding maternal mortality and morbidity.

Our project, which began in 2004, planned to build on these previous strategies and go beyond the implementation of evidence alone to assess the effect of a more far-reaching intervention of identifying evidence needs; training and support in evidence generation, synthesis and use; and provision of research infrastructure to facilitate these evidence-based practice activities.

Rationale for this project

It has been stated that 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 [13]. Information provision alone however is not enough: we need to ensure that clinical practice changes in response to that information. While little is known about the best ways to change the behaviour of healthcare workers and so to implement available evidence, we do know that it is a complex process requiring access to information, skills to interpret that information and a sense of having contributed to the process. The Cochrane Collaboration has had success in the developed world in involving clinicians in the process of generating, synthesising and using evidence. The intervention in this project will draw on the experience of the past 10 years in building the Cochrane Collaboration through infrastructure provision, training, support and methodological development and will involve local researchers to ensure the intervention is regionally appropriate and designed to increase capacity within SE Asia.

In order to increase the uptake of effective treatments and stop the use of harmful ones, it is essential that healthcare communities within SE Asia are the drivers of the project. This includes promoting interventions that are locally appropriate, identifying important research questions, conducting relevant research and evidence synthesis,

and training local practitioners in the implementation of research findings. It has been demonstrated that a sense of local ownership of projects and processes aiming to improve practice, including evidence generation, contributes to the success of implementing evidence [14].

In 2001, the Thai Cochrane Network, based at Khon Kaen University, became the first registered group of the Cochrane Collaboration in SE Asia and provides the ideal platform from which to launch this current initiative. To maximise the potential of this intervention we plan to build upon existing partnerships and organisations to extend current capacity [15].

Aims and objectives

The project was designed to address the following broad scientific question: Can the health of mothers and babies in Thailand, Indonesia, the 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 objectives of the project were intended to answer the following questions as components of the broad question:

1. What is the current teaching and practice related to pregnancy and childbirth in SE Asia?
2. What are the local barriers to the use of research in SE Asia and how can these barriers be overcome?
3. Will targeted interventions to build capacity for the generation, evaluation, synthesis and implementation of relevant evidence lead to improved research output, research implementation and better health outcomes for women and babies in SE Asia?

Methods/Design

The SEA-ORCHID project was designed as a before-after study, using action research to design and implement the intervention. It set out to extend and benefit from existing networks. The project was planned to be conducted across seven nodes, four in SE Asia and three in Australia (Table 1). Each SE Asian study node was planned to be established within an existing department of obstetrics and gynaecology or neonatology and was intended to form both the project co-ordination centre and the focus for evidence-based practice activities within the region.

Activities and timelines for each project phase are outlined in the following sections and summarised in Table 2. A SEA-ORCHID project meeting was planned to be held annually to review progress and strengthen regional collaborative networks, and was intended to be timed to coincide with a local event (eg. perinatal meeting, hospital seminar) to enhance promotional opportunities and maximise the benefits of having several international speakers present.

Pre study phase (2004)

During this phase of the study, we planned to establish three Australian support nodes and a project node within each of the four SE Asian participating countries. Under the supervision of the local SEA-ORCHID investigator, each node put in place the infrastructure to support and sustain the project. This involved purchasing equipment, employing and training staff, and seeking local ethics approval. As part of efforts to promote the project we set up a dedicated website (www.seaorchid.org) that includes information about the project; a library of project materials, resources and presentations; and a secure data-entry system.

First SEA-ORCHID project meeting

The investigators planned to meet in Malaysia before the start of the pre-intervention phase to ensure all nodes were functioning smoothly, and to plan the development of the data collection assessment tools, the training of local fieldworkers in web-based data entry and finalise project procedures.

Pre-intervention phase (2005)

The principal activities during this phase were the collection of baseline data and the recruitment and training of staff who were delivering the intervention. Three categories of information were planned to be collected at baseline and post-intervention:

1. **Adherence to recommended clinical practices and health outcomes (primary outcomes)**

We planned to assess whether current clinical practice during pregnancy and childbirth follows best-practice recommendations, and assess the impact of some these practices on the health of mothers and babies. Adherence to 12 areas of current recommended clinical practice and 13 health outcomes of mothers and babies in the four SE Asian centres were the primary outcome. The various practices and their associated health outcomes were selected on the basis of clear evidence from Cochrane systematic reviews (Table 3).

Data related to the primary outcome were planned to be collected by field-workers over a nine-month period from the consecutive case reports of 1000 women admitted to each of the participating SE Asian hospitals. Specially designed data collection forms were designed to ensure the information was extracted regarding the use of recommended practices, if applicable, together with the subsequent health outcomes of the mother and baby.

2. Current involvement in evidence-based practice (secondary outcome)

We planned to determine the level of activity and involvement in generating, teaching and using evidence at each SE Asian node by:

- identifying current research projects relevant to pregnancy and childbirth (from government funding bodies, ethics committees and research registers)
- identifying local clinical practice guidelines related to pregnancy, childbirth and infant care (through a survey of health departments and clinical associations)
- assessing the amount of undergraduate medical teaching related to evidence-based practice (through a survey of medical schools)

In addition, we planned to assess the contribution of SE Asians to the Cochrane Collaboration with respect to numbers of reviews and contributors (through a search of *The Cochrane Library*).

3. Potential local barriers to practice change (secondary outcome)

The investigators and fieldworkers planned to carry out a series of surveys and interviews within the participating institutions to establish current knowledge, attitudes and extent of evidence-based practice and the factors specific to that node which may form a barrier to practice change, or may be used to enhance practice change. Specific knowledge and beliefs about evidence-based practice, research results and systematic reviews were assessed, along with perceived difficulties in accessing, appraising and using research-based information. Culturally specific barriers to the use of the selected pregnancy and childbirth healthcare practices were explored, and any relevant issues used to modify the intervention.

Data management and analysis

A customised, secure database was designed to be housed on the project website to allow fieldworkers to enter the extracted information on data collection forms directly into the database (www.seaorchid.org). The analysis plan for the baseline data included descriptive statistics to provide a picture of current clinical practices and health outcomes in the management of pregnancy and childbirth at the four SE Asia nodes. Continuous variables were to be presented as means and standard deviations (or medians and ranges if data are not normally distributed) and dichotomous variables presented as numbers and frequencies of events.

Preparing for the intervention

Twelve educational training lecturers (educators), nine from the SE Asian participating hospitals and one at each of the Australian support nodes were recruited and trained, and materials developed for use in the training components of the intervention. A fellowships program was planned to enable health professionals and researchers from SE Asia to visit Australia to receive advanced training in the skills of evidence-based practice, guideline development, critical appraisal and systematic reviewing. These fellowships were advertised in the four SE Asian countries, and the recipients selected by the SE Asian investigators.

Second SEA-ORCHID project meeting

The investigators and educational training lecturers planned to meet in the Philippines towards the end of the pre-intervention phase to review baseline findings and to finalise the intervention, taking into consideration the barriers to practice change identified by the baseline questionnaires and interviews. Following this meeting, the Australian-based educational trainers planned to carry out the first SE

Asia teaching tour, conducting training events with the local training lecturer. This was the beginning of the intervention phase.

Intervention phase (2006 – mid 2007)

The planned intervention can be divided into the following categories with the timing of delivery according to the project schema in Table 2:

i) **Training:** The provision of training to support various evidence-based practice initiatives is a major component of the intervention being tested. Local researchers and clinicians planned to conduct training with the support of the Australian-based project members through the provision of materials and teaching assistance. Training will comprise of a fellowships program, teaching tours of all four SE Asian nodes by the Australian-based trainers in partnership with local trainers, and five project meetings. Activities will focus around three core groups:

1. Generators of evidence and evidence-based materials

The emphasis is on setting up training programs in critical appraisal, systematic reviewing and guideline development. The Cochrane Collaboration takes great pride in the quality and relevance of its training programs, and the Australian investigators have all been involved in the development and delivery of training in evidence-based practice for many years. We have access to an array of training methods and tools that have been tried and tested cross-culturally and in a variety of formats.

2. Users of the evidence: clinicians and policy makers

We planned to conduct training for clinicians in using *The Cochrane Library* and *WHO Reproductive Health Library*; implementing and using guidelines; and accessing and interpreting evidence. Training will be

open to all disciplines involved in the management of the mothers and babies unit (ie. medicine, nursing, community health workers). For policy makers we plan to conduct tailored training workshops around understanding and interpreting evidence. These will be adapted from a series of workshops for policy makers developed by the Australasian Cochrane Centre and will be taught in partnership with SE Asian contributors.

3. Educators about evidence: teachers and trainers

To build capacity and to ensure the outcomes from this project are sustained and extended to other clinical areas, we planned to conduct training events targeting future clinical trainers and potential opinion leaders in SE Asia. In addition, to facilitate practice change through investment in our future clinicians, we plan to provide material and training on the principles of evidence-based practice to those involved in undergraduate programs for doctors, nurses and allied health workers. We will achieve this through existing networks linking the investigators and medical educators in SE Asia.

ii) **Systematic reviewing:** We planned to work with those providing care to women and babies in SE Asia to identify important questions for which systematic review evidence is lacking. Interventions appraised in systematic reviews were clinically relevant and culturally acceptable for the management of pregnancy and childbirth in SE Asia. These reviews were intended to be prepared with support from investigators and educators and published in *The Cochrane Library*, and the results actively disseminated to clinicians through guidelines, training events and other publications.

iii) **Guideline development:** Based on experience with developing guidelines for the Australian National Health and Medical Research Council, we planned to co-

ordinate and facilitate locally relevant evidence-based guideline development and implementation.

iv) **Infrastructure support:** Health care based on evidence requires not only trained personnel, but also physical infrastructure, for example, computers and access to information and support. This project was designed to improve research infrastructure and capacity within SE Asia to address locally relevant and culturally specific questions by providing a central focus for research activity and skills.

v) **Academic exchange:** Over the course of this project there were numerous opportunities for academic exchange. Fellowships in Australia were offered to researchers and clinicians from SE Asia, and the Australian-based educators will travel to all the nodes to conduct workshops and partner the SE Asian educational trainers in the development of materials.

vi) **Promotion:** The five project meetings were planned to be held to coincide with local clinical meetings and events. This allowed access to the SE Asian and Australian investigators as speakers at these events and assist in the promotion of evidence-based practice, the SEA-ORCHID project and the results of the research conducted. In addition, the work resulting from the project was intended to be published in the academic literature and presented at local, national and international perinatal meetings and Cochrane Colloquia.

vii) **Input into the undergraduate curriculum:** We planned to facilitate teaching of evidence-based practice skills in medical, nursing and allied health schools by sharing knowledge, skills and materials from Australia together with content relevant to SE Asia. This was intended to be facilitated based on the audit of evidence-based practice learning gathered as part of the baseline data collection.

Third SEA-ORCHID project meeting

A larger meeting involving the investigators, educational trainers and SEA-ORCHID fellows was planned to be held in Thailand. This meeting intended to review progress with the intervention, identify potential future research projects based on identified research needs, and consider opportunities for funding beyond the project to sustain the SE Asian nodes and evidence-based practice activity. Again, immediately following the meeting, Australian educational trainers planned to undertake a tour to support local educators in training events.

Outcome assessment phase (mid 2007 - mid 2008)

The methodology of outcome assessment was designed to duplicate that of the baseline data collection, with SE Asian fieldworkers recruited and trained to carry out the tasks overseen by the local investigators, and facilitated through a web-based data collection system.

Primary outcome

The primary indication of the value of the intervention was planned as changes in the process of care during pregnancy and childbirth and any associated impact on health outcomes for mothers and babies. Adherence to recommended practice and maternal/neonatal outcomes (Table 3) were recorded from consecutive case records (1000 per participating hospital) over a nine-month period in a similar fashion to that of the baseline data collection. Descriptive statistics were intended to be used to summarise the data and changes from baseline to endpoint calculated for all measures in an effort to demonstrate practice change and improvement in health.

Secondary outcomes

The following activities were planned to be re-assessed in a similar way as at baseline and compared:

a) Involvement in evidence-based practice activity

b) Knowledge and beliefs and the potential barriers to practice change

c) SE Asian contribution to the work of the Cochrane Collaboration

In addition, sustainability of activities beyond the project through procurement of future research funding was intended to form a measure of the impact of the intervention.

Fourth SEA-ORCHID project meeting

The investigators and trainers planned to meet in Indonesia to review the intervention phase and ensure the project teams are prepared for the post-intervention data collection. There was also planned to be a focus on sustaining the activities initiated during the SEA-ORCHID project once funding ends, and planning for future intra- and inter-regional collaborations and partnerships.

Reporting phase (mid 2008)

Dissemination of results will be an integral feature of the project and we anticipate the following publications:

- management of pregnancy and childbirth in SE Asia prior to the intervention
- perceived barriers to clinical practice change in SE Asia
- several systematic reviews and clinical practice guidelines relevant to the management of pregnancy and childbirth in SE Asia and other resource poor settings
- experiences of training in partnership across cultures
- final report and publications regarding the effect of the intervention

Fifth SEA-ORCHID project meeting

The final conference will be attended by the investigators and will focus on interpretation of the analysed results, planning final reports and associated publications, and planning future work in SE Asia.

Discussion/Conclusion

Basing healthcare practice and policy on evidence ensures the maximal benefit for investment. This is important in all communities but particularly when resources are low and the threats to health are large. This project has the potential to impact significantly on the health of mothers and babies in SE Asia by improving care during pregnancy and birth. Resulting from this project, we anticipate that within SE Asia there will be enhanced capacity to:

- train existing and future clinicians to interpret and implement evidence
- ensure locally relevant evidence is available and accessible
- identify important questions yet to be answered and so take a cost effective and high impact approach to future research funding
- base policy decisions on research findings
- develop and implement local clinical practice guidelines
- contribute more relevant systematic reviews for Cochrane Library

The possible benefits, however, extend beyond maternal and newborn care as at the end of this project there will be an existing network of SE Asian researchers and clinicians with the capacity to generalise this model to other health priority areas. It is anticipated that this project will facilitate the ongoing development of evidence-based practice and policy in SE Asia through attracting additional long term funding, expansion into community-based care and the establishment of nodes in other countries in the region.

Abbreviations

SE Asia – South East Asia

SEA-ORCHID – South East Asia Optimising Reproductive and Child Health in Developing Countries

UNDP – United Nations Development Programme

UNFPA – United Nations Population Fund

UNICEF – United Nations Children's Fund

WHO – World Health Organization

Competing interests

The authors declare they have no competing interests.

Authors' contributions

DH-S, PL, SG and CC conceived the study and participated in the project design. All authors were involved in the development of the design of the project, drafting of the manuscript and revising it critically for important intellectual content and have given final approval of the version to be published.

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Table 1: SEA-ORCHID project nodes and participating SE Asian hospitals

Country	Node	South East Asian Hospitals	Investigator
Thailand	Department of Obstetrics and Gynaecology, Khon Kaen University, Khon Kaen	Srinagarind Khon Kaen University Hospital Khon Kaen Regional Hospital Kalasin General Hospital	Pisake Lumbiganon
Philippines	Department of Obstetrics and Gynecology, College of Medicine, University of the Philippines Manila, Manila	Philippine General Hospital (University of the Philippines) Dr. Jose Fabella Memorial Hospital	Mario Festin
Malaysia	Department of Paediatrics, Royal College of Medicine, Ipoh	Ipoh Hospital, Perak Universiti Sains Malaysia, Kota Bharu	Jacqueline Ho
Indonesia	Department of Obstetrics and Gynecology, Gadjah Mada University, Yogyakarta	Dr. Sardjito Hospital Sleman District Hospital	Mohammad Hakimi
Australia	NSW Centre for Perinatal Health Services Research, Sydney		David Henderson-Smart
Australia	Australasian Cochrane Centre, Monash University, Melbourne		Sally Green
Australia	Australian Research Centre for the Health of Women and Babies, Discipline of Obstetrics and Gynaecology, University of Adelaide, Adelaide		Caroline Crowther

Table 2: SEA-ORCHID project plan and activities associated with each phase

	Year	Australian Support Centres	SE Asian Study Nodes
Pre Study Phase	**2004**	*First SEA-ORCHID project meeting Malaysia: focus on planning, and development of assessment tools*	
		Recruit project manager: five year appointment	Recruit project supervisor (Thailand): five year appointment
		Recruit project administrator five-year appointment	Recruit project administrator (Thailand): five year appointment
		Develop data extraction and recording tools for primary and secondary outcomes	Set up project nodes
		Set up and pilot web-based forms and data entry system	Obtain ethics committee approval from local institutions
		Obtain ethics committee approval	Begin promotion of project within SE Asian nodes
			Recruit and train four SE Asian fieldworkers
Pre-intervention	**2005**	Data cleaning and ongoing analysis from web-based system as data entered from nodes	Carry out baseline data collection of primary and secondary outcomes (data entry via web)
		Recruit and train three educators/systematic reviewers/guideline developers (one at each support centre): three year appointment	Recruit and train nine educators/guideline developers/systematic reviewers from participating hospitals
		Host training of SE Asian educators	Plan and organise training events and associated local promotion
		Develop training materials	Advertise and select eight fellows for Australian fellowships in 2006
		Measure baseline involvement of SE Asia in Cochrane Collaboration	
		Second SEA-ORCHID project meeting the Philippines: review and report findings from baseline data collection and adapt intervention to ensure it addresses identified barriers to change	
		Conduct teaching tour	
Intervention	**2006 to mid 2007**	Ongoing support for training in systematic reviews and EBP	Conduct training in systematic reviewing and EBP and undertake systematic reviews
		Partner in guideline development	Develop guidelines
		Host eight SE Asian fellowships	Disseminate the evidence from Cochrane reviews
		Support SE Asian nodes in all activities	Identify local priorities for reviews
		Third SEA-ORCHID project meeting Thailand: focus on developing undergraduate programs and planning for funding beyond project to sustain nodes	
		Two teaching tours (one adjacent to SEA-ORCHID project conference)	
Outcome Assessment	**mid 2007 to mid 2008**	Provide all data extraction and recording tools	Recruit and train four fieldworkers for outcome assessment
		Outcome assessment of SE Asian involvement in Cochrane Collaboration	Complete collection of primary and secondary outcome data (data entry via web)
		Data monitoring, cleaning and analysis	
		Fourth SEA-ORCHID project meeting Indonesia: review outcome assessment, plan for activities beyond employment of trainers	
Report	**End 2008**	*Fifth SEA-ORCHID project meeting (investigators) interpret analyses, plan final reports and assist with planning of future initiatives*	
		Write up of final reports and associated publications	

Table 3: Health-related outcomes

Recommended practice	Outcome intended to reduce
Beneficial forms of care	
Antibiotics for preterm prelabour rupture of membranes (pPROM)[16]	Chorioamnionitis; neonatal sepsis
Corticosteroids prior to preterm birth[17]	Neonatal death; complications of preterm birth
External cephalic version for breech presentation at term[18]	Caesarean section rate; birth trauma
Continuous support during labour[19]	Caesarean section rate
Magnesium sulphate for eclampsia and pre-eclampsia[20, 21, 22]	Maternal death; eclampsia
Active management of third stage of labour[23]	Postpartum haemorrhage; maternal death
Intraoperative antibiotics during caesarean section[24]	Maternal infection
Vacuum extraction (versus forceps) for operative delivery[25]	Perineal injury; postpartum haemorrhage
Immunisation for Hepatitis B[26]	Hepatitis B infection
Forms of care likely to be harmful	
Routine episiotomy[27]	Perineal injury; maternal infection
Routine shaving*[28]	Maternal infection
Routine enemas*[29]	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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The outcomes of midline versus medio-lateral episiotomy

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Abstract

Background

Episiotomy is the surgical enlargement of the vaginal orifice by an incision of the perineum during the second stage of labor or just before delivery of the baby. During the 1970s, it was common to perform an episiotomy for almost all women having their first delivery, ostensibly for prevention of severe perineum tears and easier subsequent repair. However, there are no data available to indicate if an episiotomy should be midline or medio-lateral. We compared midline versus medio-lateral episiotomy for complication such as extended perineal tears, pain scores, wound infection rates and other complications.

Methods

We conducted a prospective cohort including 1,302 women, who gave birth vaginally between April 2005 and February 2006 at Srinagarind Hospital—a tertiary care center in Northeast Thailand. All women included had low risk pregnancies and delivered at term. The outcome measures included deep perineal tears (including perineal tears with anal sphincter and/or rectum tears), other complications, and women's satisfaction at 48 hours and 6-weeks postpartum.

Results

In women with midline episiotomy, deep perineal tears occurred in 14.8%, which is statistically significantly higher compared to 7% in women who underwent a medio-lateral episiotomy (p-value<0.05). There was no difference between the groups for other outcomes (such as blood loss, vaginal hematoma, infection, pain, dyspareunia, and women's satisfaction with the method). The risk factors for deep perineal tears

were: midline episiotomy, primiparity, maternal height <145 cm, fetal birth weight >3,500 g and forceps extraction.

Conclusions

Midline compared to medio-lateral episiotomy resulted in more deep perineal tears. It is more likely deep perineal tears would occur in cases with additional risk factors.

Background

Episiotomy is the surgical enlargement of the vaginal orifice by an incision of the perineum during the second stage of labor or just before delivery and requires repair by suturing [1]. During the 1970s, episiotomies were performed on almost all women having their first delivery in order to prevent severe perineal tears and make repair easier. Another commonly cited but unproven benefit of routine episiotomy was the prevention of pelvic relaxation. A number of observational studies and randomized trials showed that routine episiotomy is associated with an increased incidence of anal sphincter and rectal tears [2].

In the Cochrane Database of systematic reviews 1999, restrictive rather than routine use of episiotomy was recommended; however, no indications were given vis-à-vis which type should be used and when, i.e., for assisted vaginal delivery (forceps or vacuum), preterm delivery, breech delivery, predicted macrosomia or a presumed imminent tear. However, we could not identify a clinical trial comparing medio-lateral versus midline episiotomy [3]. At Srinagarind Hospital, our personnel are encouraged to use restrictive episiotomy and to select the type appropriate for each case.

We aimed to evaluate midline versus medio-lateral episiotomy for deep perineal tears, pain scores, wound infection rate and other complications at 48-hours and 6-weeks postpartum.

Methods

This was a prospective cohort study for which we recruited 1,302 pregnant women who gave birth vaginally at Srinagarind Hospital, Khon Kaen University—a tertiary care center in Northeast Thailand—between April 2005 and February 2006. These women had low risk pregnancies according to the following criteria: singleton, cephalic presentation and term pregnancy. All women received episiotomy, either midline or medio-lateral according to attending personnel. Women with spontaneous perineal tears, epidural analgesia and/or any underlying disease (such as diabetes mellitus, chronic renal disease or immune deficiency related diseases) were excluded.

We collected some of the study data from the medical records. The primary outcome was deep perineal tear, defined as a tear with anal sphincter and/or rectum tearing and assessed by the attending physician(s) or nurse(s). The amount of blood loss was estimated by the delivery attendants, based on visual inspection.

Forty-eight hours postpartum the women were asked to complete a pain scoring form after having signed informed consent. We used pain scoring scale of 0 to 10 for 'none' to 'severe' pain regarding the episiotomy wound. Six weeks postpartum, women were interviewed either during the postpartum visit or by telephone for assessment of perineal pain, wound infection, dyspareunia and their satisfaction with the procedure.

We used STATA 9.0 software for Windows (STATA Corp., College Station, TX) for data processing and analysis. Results were reported as means, standard deviations (SD), medians, ranges, relative risks (RR) and 95% confidence intervals (CI).

This study was approved by the Human Research Ethics Committee of Khon Kaen University.

Results

Of the 1,302 pregnant women studied, 426 received midline and 876 medio-lateral episiotomy. The baseline characteristics of the two groups are shown in terms of maternal age, weight before delivery, height, parity, gestational age, duration of second stage of labour, fetal birth weight, birth asphyxia, perineal repairing time, amount of blood loss, type of vaginal delivery, type of personnel who performed the delivery and use of antibiotic prophylaxis (Table 1).

Deep perineal tears occurred in 63 of the 426 women with midline episiotomy (14.79%), and in 61 of 876 women with medio-lateral episiotomy (6.97%) (p-value<0.05). There was no statistically significant difference in blood loss (median 200 ml, range 50-100 ml in the midline versus median 200 ml, range 50-900 ml in the medio-lateral group) and vaginal hematoma complications after delivery (2/426 for midline versus 1/876 for medio-lateral episiotomy).

We were able to assess pain scores and wound infection 48 hours postpartum for 222 of 426 women with midline and 536 of 876 women with medio-lateral episiotomies. There was no difference in pain scores at 48 hours postpartum between the two

groups (mean 3, range 0-8 in the midline versus mean 3, range 0-9 in the medio-lateral group). One case with wound infection occurred in the medio-lateral episiotomy group.

Among the women studied, we were able to contact with 312 women (24.0%) 6-weeks postpartum to assess outcomes. We found no statistically significant difference between the two groups, regarding pain scores (median 0, range 0-1 in the midline versus Median 0, range 0-5 in the medio-lateral group, p-value 0.13) and satisfaction with the episiotomy procedure (100% in the midline versus 99.1% in the medio-lateral group). There were five women with midline and 19 with medio-lateral episiotomies that had sexual intercourse before six weeks postpartum. There was no difference in dyspareunia between the two groups (0/5 in the midline versus 3/19 in the medio-lateral group) and none of them had any wound infection.

The following risk factors were associated with deep perineal tear: (1) underwent a midline episiotomy (RR 2.12; 95% CI 1.52 to 2.96); (2) primiparity (RR 3.47; 95% CI 2.27, to 5.31); (3) maternal height ≤145 cm (RR 2.60; 95% CI 1.19 to 5.67); (4) vacuum extraction (RR 1.92; 95% CI 1.17 to 3.15); (5) forceps extraction (RR 4.04; 95% CI 2.70 to 6.04); and, (6) duration of second stage of labour >60 minutes (RR 2.30; 95% CI 1.17 to 4.54). We controlled for confounders of the factors affecting deep perineal tears by using a multivariate analysis. The only statistically significant factors were: (1) midline episiotomy (RR 1.94; 95% CI 1.25 to 2.99); (2) primiparity (RR 3.56; 95% CI 2.23 to 5.69); (3) maternal height ≤145 cm (RR 4.22; 95% CI 2.01 to 8.44); (4) fetal birth weight >3500 g (RR 2.22; 95% CI 1.46 to 3.38); and, (5) forceps extraction (RR 2.82; 95% CI 1.89 to 4.19)(Table 2).

Discussion

In this cohort study, 1,302 low risk pregnant women were studied for outcomes related to midline and medio-lateral episiotomies. We found that midline episiotomy resulted in a greater rate of deep perineal tears than medio-lateral episiotomies (14.8% versus 7 %) but there was no difference between the two groups on other outcomes such as blood loss, hematoma, infection, pain and dyspareunia.

The results of our study are comparable to previous reports regarding deep perineal tears; specifically, Aytan *et al.* found severe perineal lacerations in 3% of midline versus 1% of medio-lateral episiotomies [4] and Angioli *et al.* reported 6.6% in midline versus. 4.1% in medio-lateral episiotomies [5].

We found that the risk factors of deep perineal tears were midline episiotomy, primiparity, maternal height ≤145 cm, baby's birth weight >3500 g and forceps extraction. Again, our results are similar to those from previous studies [6-13].

Interestingly, Werner *et al.* reported that midline episiotomy actually had less hematoma formation and blood loss [12] while we found that vaginal hematoma was the only complication which occurred in the two groups (not statistically different between groups). This is a rare complication and our study might not have had the power to detect the difference.

Coats *et al.* compared midline and medio-lateral episiotomies in a randomized controlled trial and found no difference in perineal pain immediately and 3 months

postpartum [9], comparable to our results. By comparison, Werner *et al.* found significantly less pain after midline than medio-lateral episiotomies on the third day postpartum [12]. A limitation to our study might be pain assessment since the proportion of women who gave informed consent and completed the pain scoring form 48 hours postpartum was low and most of our results were drawn from telephone interviews 6-weeks postpartum.

Our study found only one case of wound infection in the medio-lateral episiotomy group at 48 hours which was absent at 6-weeks postpartum. A previous study by Larsson *et al.* assessed perineal problems after episiotomy versus spontaneous perineal laceration and found a significantly higher rate of infection in the episiotomy group [14]. But like our results, Harrison *et al.* found no case of infection for the first four days after delivery or at the 6 week postpartum check-up [15]. By way of corroboration, Owen and Hauth retrospectively reviewed women who had given vaginal birth at the University of Alabama Hospitals and found only ten cases of postpartum perineum infection among 20,713 deliveries, with all of the infectious complications occurring after midline episiotomy [16].

We found that almost all women in both groups were satisfied with their perineum scar. Fewer women in the midline group complained about dyspareunia compared to the medio-lateral group (0 versus 15.8%, respectively); however, we cannot absolutely conclude that one is better due to the small number of participants who had sexual intercourse within the 6-weeks postpartum period. A previous report indicated midline incision was preferable to medio-lateral episiotomy vis-à-vis sexual function, healing, and improved appearance of the perineal scar [17]. However, in our study, we cannot make strong conclusions regarding long-term effects due to the high rate of

loss-to-follow-up. Furthermore, in our study, there was no difference on the effect of episiotomy type on blood loss. Theoretically, the line of incision in a midline episiotomy stays within an area where the muscles of the perineum from both sides connect, which should limit blood loss [12]. Additionally, we may have underestimated blood loss by depending on visual inspection instead of using a more objective measuring method. However, we may need randomized controlled trial study to assess the accuracy of the method to estimate blood loss.

Our study may not have been able to account for all possible factors, with a randomized controlled trial being the preferred study design to compare different interventions.

Conclusions

In this cohort study we would conclude that midline episiotomies resulted in more cases of deep perineal tear compare to medio-lateral episiotomies. Further, deep perineal tears may occur more frequently in cases with additional risk factors. Although a randomized controlled trial (RCT) is the preferred study design to compare different interventions, we were unable to conduct a RCT in our setting. However, the results of our cohort study can pave the way to conduct a well-designed RCT, comparing midline versus medio-lateral episiotomy.

Competing interests

No competing interest.

Authors' contributions

Sooklim R and Thinkhamrop J made substantial contributions to the conception and design, acquisition of data, analysis and interpretation of data; Sooklim R, Pitak P and Chansamak S had contribution on data collection; Sooklim R, Thinkhamrop J, Lumbiganon P, Prasertcharoensuk W, Pattamadilok J, Chongsomchai C and Seejorn K were involved in the drafting and revising of the manuscript; Thinkhamrop J and Seejorn K finalized the version to be published.

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Table 1 Baseline characteristic of the pregnant women studied

Characteristics	Midline episiotomy (n=426)	Medio-lateral episiotomy (n=876)
Age (yr, median, min-max)	28 (16-44)	26 (12-47)
Weight before delivery (kg, median, range)	64 (44.3-93.2)	64.8 (45.4-96.3)
Height (cm, mean±SD)	156.7±5.0	156. ±5.2
Gravidity (No., mean±SD))	1.9±0.9	1.7±0.9
Nulliparous (No., %)	206 (48.4)	488 (55.7)
Multiparous (No., %)	220 (51.6)	388 (44.3)
Gestational age (wks, mean±SD)	38.7±1.3	38.9±1.2
Duration of 2nd stage (min, median, min-max)	13 (1-111)	14 (1-140)
Baby birth weight (gm, mean±SD)	3,104.4 ±346.5	3,147±383.9
Birth asphyxia. (No., %) (Apgar score at one minute ≤7)	14(3.3)	64(7.3)
Suture's time (min, mean±SD)	22.75±11.40	26.15±12.89
Estimate blood loss (ml, median, min-max)	200 (50-1,000)	200 (50-900)
Type of delivery. (No., %) 1. normal delivery 2. forceps extraction 3. vacuum extraction	 379 (88.9) 22 (5.7) 25 (5.9)	 734(84.8) 49(5.6) 84(9.6)
Delivery performed by (No., %) 1. intern 2. resident 3. staff	 5(1.2) 155(36.4) 266(62.4)	 57(6.5) 725(82.8) 94(10.7)
Suture material. (No., %) 1. polyglycolic acid	 28(6.6)	 57(6.5)

2. non polyglycolic acid 3. combined	369(86.7) 29(6.8)	816(93.2) 3(0.3)
Antibiotic prophylaxis at LR (No., %)	28(6.6)	44(5.1)

Table 2 Risk factors of deep perineal tear

Risk factors	Univariate analysis RR (95% CI)	Multivariate analysis RR (95% CI)
Midline episiotomy	2.12 (1.52, 2.96)*	1.94 (1.25, 2.99)*
Maternal age >35 yrs., <20 yrs.	0.81 (0.49, 1.33)	0.94 (0.56, 1.59)
Primiparity	3.47 (2.27, 5.31)*	3.56 (2.23, 5.69)*
Gestational age >41 wks.	0 (α, α)	8.39 (0, α)
Maternal height ≤145 cm.	2.60 (1.19, 5.67)*	4.22 (2.01, 8.44)*
Maternal body mass index >25	0.94 (0.65, 1.36)	1.01 (0.96, 1.06)
Baby birth weight > 3500 gm.	1.51 (0.99, 2.27)	2.22 (1.46, 3.38)*
Experienced Physician		
1. intern	2.50 (0, α)	9.45 (0, α)
2. resident	0.48 (0.34, 0.67)	0.69 (0.44, 1.08)
3. staff	1	1
Operative vaginal delivery		
1. vacuum extraction	1.92 (1.17, 3.15)*	1.12 (0.62, 2.00)
2. forceps extraction	4.04 (2.70, 6.04)*	2.82 (1.89, 4.19)*
3. normal vg. Delivery	1	1
Duration of second stage >60 min	2.30 (1.17, 4.54)*	1.69 (0.81, 3.54)

*statistically significant

Int J Gynecol Cancer 2007

One-year follow-up of single-visit approach to cervical cancer prevention based on visual inspection with acetic acid wash and immediate cryotherapy in rural Thailand

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Abstract. Chumworathayi B, Srisupundit S, Lumbiganon P, Limpaphayom KK. One-year follow-up of single-visit approach to cervical cancer prevention based on visual inspection with acetic acid wash and immediate cryotherapy in rural Thailand. *Int J Gynecol Cancer* 2007.

The aim is to evaluate 1) the visibility of cervical squamocolumnar junction (SCJ) after cryotherapy treatment and 2) to evaluate the effectiveness of cryotherapy treatment originally performed as part of a safety, acceptability, and feasibility (SAFE) demonstration project evaluating the SAFE of visual inspection with acetic acid (VIA) followed by immediate offer of cryotherapy among those who were tested positive and eligible for treatment. A total of 704 women presented at 1-year follow-up exam during which VIA was performed again by nurses. Six hundred and forty eight (92.0%) women received colposcopy and any kind of biopsy, if indicated, by trained physician colposcopists at a referral hospital. At 1 year, VIA nurses assessed 42 of 648 referred women (6.5%) as abnormal (test positive or suspected cancer). The SCJ was visible to the colposcopists in 91.7% (594/648) of the women. Among 42 women assessed as abnormal by the nurses, colposcopic findings were abnormal in 83.3% (35/42), with one low-grade squamous intraepithelial lesion, two high-grade squamous intraepithelial lesion (HSIL), and one adenocarcinoma confirmed later by biopsy. Among 606 VIA negative women, colposcopy was abnormal in only 23.4% (142/606), with two cases of HSIL confirmed later. Given that the SCJ was visible in the vast majority of women (91.7%) after cryotherapy, VIA could be used to provide follow-up for women previously treated. The disease negative rate after cryotherapy (no human papillomavirus infection, no cervical intraepithelial neoplasia, and no cancer) at 1 year after treatment was 85.5% (554/648).

KEYWORDS: cervical neoplasia, colposcopy, cryotherapy, VIA, visual inspection with acetic acid.

Supported by overwhelming data, human papillomavirus (HPV) infection is currently known as the necessary cause of cervical cancer. This information has permitted the development of various screening techniques, including HPV testing. However, the challenge is to choose the appropriate screening test and link it with effective feasible treatment to complete the circle of effective cervical cancer prevention programs, especially in low-resource settings. HPV testing is still too expensive to be used in public health-based screening program in low-resource settings. Papanicolaou (Pap) smear, the cytology-based screening test most commonly used in developed countries, requires multiple visits at regular intervals, sufficient number of cytopathologists, and complex laboratory infrastructures.

Thai Ministry of Public Health Ethics Review Committee Approval Date: October, 22, 1999.
This study is a part of "Safety, acceptability, and feasibility of a single-visit approach to cervical cancer prevention in rural Thailand: a demonstration project" by "Royal Thai College of Obstetricians and Gynaecologists (RTCOG)/JHPIEGO Corporation Cervical Cancer Prevention Group," that was published in "*Lancet* 2003;**361:**814–20," and was presented in the Ninth Biennial Meeting of the International Gynecologic Cancer Society (IGCS), October 20–24, 2002, Seoul, South Korea, by Clinical Professor Somkeart Srisupundit. Abstract of this article was also previously published in *International Journal of Gynecological Cancer* 2002;**12:**592.

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In low-resource settings where materials and human resources are low, the main emphasis should be placed on the extent of coverage (more than 80% of target population)[1] rather than on the frequency of examinations (every 1, 3, or 5 years) and using more sensitive screening tests. A highly specific but moderately sensitive screening test in cervical cancer detection, such as Pap smear[2], is most useful in settings where prevalence of the disease is low, which is not the case of many low-resource settings such as Thailand, where prevalence of HPV infection and incidence of cervical cancer is high[3].

Visual inspection with acetic acid (VIA) has an acceptable test performance for population-based cervical screening[4]. It is useful for detection of precancerous lesions of cervical cancer not only in low-resource settings but also in well-equipped health centers and cancer centers. In those nonlow-resource settings, VIA has a positive predictive value comparable to the conventional Pap smear, but it is more likely to achieve earlier diagnosis, follow-up, and treatment than cytology-based screening[5]. Recently, there are many reports confirming that VIA is more sensitive but less specific[6–10] when compared with Pap smear. Because of its low specificity, around 20% of the referred cases are false positive.

However, VIA when combined with cryotherapy as a single-visit approach has been proposed as the most promising alternative[11]. It can close the circle of prevention by immediate safe cryotherapy treatment offered. VIA permits the identification of acetowhite lesions, evidence of epithelial changes caused by dehydration of high-protein large-nuclei cells after exposure to acetic acid. This process is generally found in cells that have been invaded by HPV, causing them to show a white color after acetic acid wash.

Because there was no previous information about cervical appearances and histologic findings at 1 year after cryotherapy and as a part of quality assurance in our safety, acceptability, and feasibility (SAFE) demonstration project[11], we performed colposcopic follow-up and assessed the results of treatment originally performed as part of a demonstration project of VIA followed by immediate offer of cryotherapy among those who were tested positive and eligible for treatment.

Materials and methods

Volunteers

This study was conducted in Roi-Et province, northeast Thailand. The protocol was approved by the Thai Ministry of Public Health Ethics Review Committee and all women gave their signed, informed consent prior to enrollment in the study. These women were recruited during the SAFE demonstration project 1 year before this follow-up visit for the prevention of cervical cancer carried out by 12 trained nurses working in four districts of Roi-Et province.

From 5999 women screened in SAFE project[11], the VIA test-positive rate was 13.3% (798/5999), and 98.5% (609/618) of those eligible accepted immediate treatment. Overall, 756 (12.6%) women received cryotherapy, 629 (83.2%) women returned for their first follow-up visit at 3–4 months after cryotherapy. No major complications were recorded. At their 1-year visit, all 756 patients were planned to have VIA test again. Regardless of the VIA result, all women were to be referred to the referral hospital for colposcopy and, if indicated, any kind of biopsy (ECC, endocervical curettage; colposcopic-directed biopsy; LEEP, loop electrosurgical excision procedure; conization; or polypectomy).

Methods

Of 756 eligible women who received cryotherapy performed by trained nurses as a result of positive VIA test, and acceptance of the offered treatment, 704 (93.1%) presented for a 1-year follow-up exam during which VIA was performed again by nurses. Fifty-six VIA negative women (8%) were lost to follow-up. However, 648 (92.0%) of these women were then referred. Six hundred and six women, with negative result, were referred to receive colposcopy and biopsy, as indicated, by trained physician colposcopists at colposcopic clinic in Roi-Et Provincial Hospital. On the other hand, 42 abnormal (positive or suspected cancer) cases were referred to Srinagarind Hospital in Khon Kaen University. All colposcopists were well trained by at least 2 years of training and registered as members of Royal Thai College of Obstetricians and Gynecologists, Thai Gynecologic Cancer Society, and Thai Society for Colposcopy and Cervical Pathology.

This study had been conducted during April 2001 through October 2001. All women were sent to colposcopic clinics within 1 month after the follow-up VIA test at 1 year. Regardless of the result, colposcopists would do colposcopic examination for every woman. Using a nonlubricated bivalve speculum, then colposcopists identified and observed the cervix. Immediately afterward, any excess mucus was cleaned away with a dry cotton swab, then colposcopy with green filter was done, and findings were recorded. Solution of 5% acetic acid was then applied to the cervix with a cotton swab and colposcopy was done again. If the squamocolumnar junction (SCJ) was totally seen and

there was no abnormal lesion on the cervix, nothing would be done except appointing her to have a cervical cancer screening examination again within the next 3 years. If the SCJ was not totally seen, even if there was no abnormal lesion on the cervix, an ECC had to be performed to guarantee that there was no lesion hidden inside cervical os. If any suspected lesion was seen, a biopsy was done at the most severe point as directed by colposcopy according to the colposcopist's opinion. If the lesion extended into the cervical os, an ECC was performed to guarantee that there was no more severe lesion hidden inside. In summary, colposcopy was planned to perform in all women with either positive or negative VIA results. Colposcopy with biopsy (ECC, colposcopic-directed biopsy, LEEP, conization, or polypectomy) was the gold standard for diagnosis, except for the one who had satisfactory normal colposcopic finding (SCJ was totally seen).

Results

A total of 704 women (93.1% of 756 postcryotherapy cases) presented for a 1-year follow-up exam during which VIA was performed again by trained nurses. Mean age was 37.96 years (SD 4.47, range 31–46). Six hundred and forty-eight (92.0%) women were then referred to receive colposcopy. These were 606 normal (93.5%) and 42 or 6.5% abnormal (41 positive and 1 suspected cancer). Six hundred and six VIA negative women were referred to Roi-Et Provincial Hospital in Roi-Et city. Meanwhile, 42 women with abnormal VIA were referred to Srinagarind Hospital at Khon Kaen University. One of these was diagnosed as a suspected cancer case (Fig. 1).

The SCJ was totally visible to the colposcopist in 91.7% (594/648) of the women. An example picture of cervix, 1 year after cryotherapy, SCJ was still easily seen, is shown in Figure 2. The rest of patients whose SCJs could not be totally seen were because SCJs were hidden inside cervical os. Abnormal colposcopic findings ranged from acetowhite lesion to atypical vessels. Among the 606 women with negative VIA, the colposcopic findings were abnormal in only 23.4% (142/606), with two cases of high-grade squamous intraepithelial lesion (HSIL) confirmed later by biopsy. SCJ could not be seen in one of these two patients. The colposcopist saw only acetowhite lesion inside os and assumed that it was only low-grade squamous

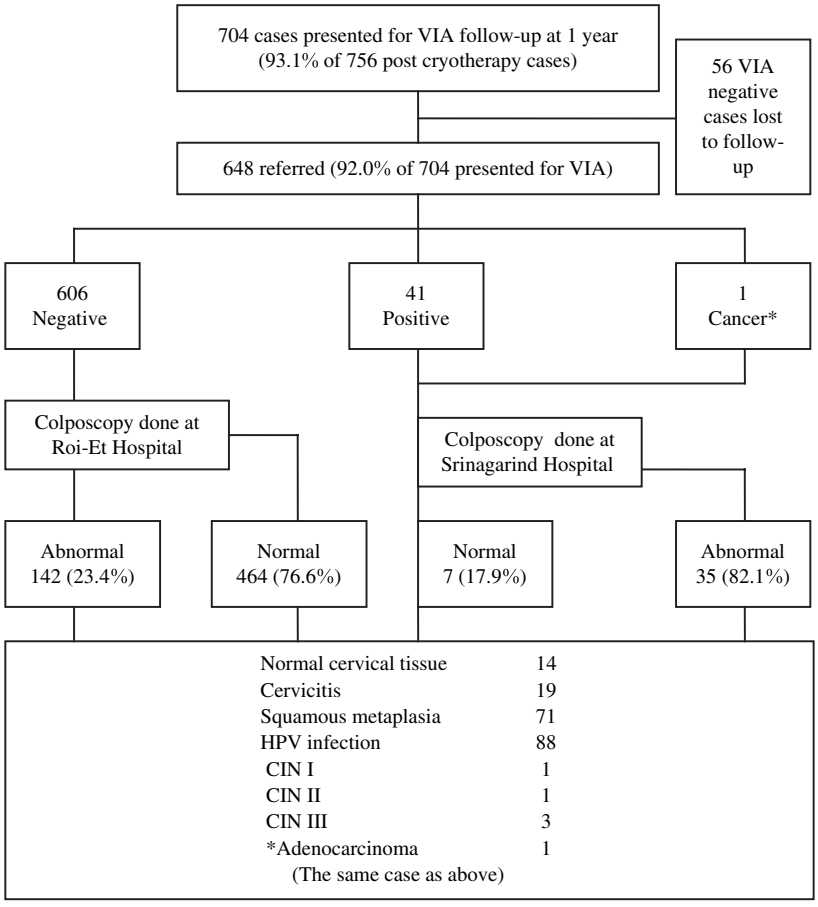

Figure 1. Management scheme of previous VIA-positive patients at 1 year after cryotherapy.

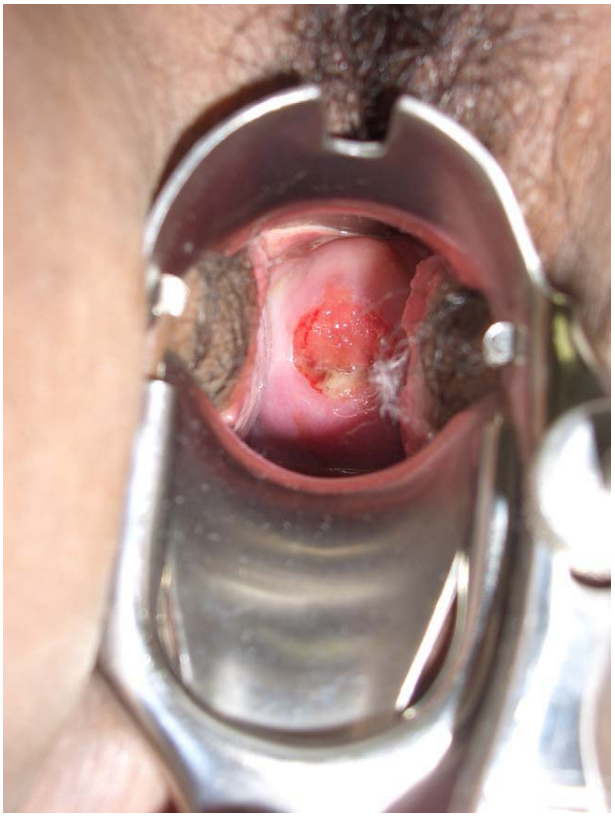

Figure 2. An example of cervix, 1 year after cryotherapy, SCJ was still easily seen.

intraepithelial lesion (LSIL). Only ECC was done and the result then turned out to be HSIL. Regarding the second HSIL patient, there was a large acetowhite lesion on cervix by colposcopy that a nurse missed when she performed VIA. Among 42 women assessed as abnormal (VIA positive or suspected cancer) by trained nurses, colposcopic findings were abnormal in 83.3% (35/42), with one LSIL (cervical intraepithelial neoplasia [CIN] I) two HSIL (one CIN II and one CIN III) and one well-differentiated villoglandular adenocarcinoma (in a polyp-stage IA) confirmed later by biopsy (Table 1).

Among the 648 women examined by colposcopy, the SCJ was totally seen and there was no abnormal lesion on the cervix of 440 women, therefore, neither ECC nor biopsy was done. Of 208 women in whom biopsy was done under colposcopy, there were 36 abnormal VIA cases and 172 normal VIA cases. In the 36 abnormal VIA cases, the final histologic-confirmed diagnosis turned out to be abnormal (LSIL, HSIL, or cancer) in 22 cases or 52.4% (22/42) of all VIA-positive cases. Predictably, in the 172 normal VIA cases, the final histologic-confirmed diagnosis turned out to be abnormal (LSIL and HSIL) in only 72 cases or 11.9% (72/606) of all VIA negative cases (Table 2).

From these data, we might say that cryotherapy failed in treating of preinvasive lesions in only five women with persistent HSIL or cancer shown in Table 2. Their ages were 33, 35, 37, 42, and 44 years. Their pathologic diagnoses were four HSIL one adenocarcinoma (in the 44-year-old patient). We have reviewed their first VIA record forms and found that all of them had large acetowhite lesions occupying about 50% of their cervices. One patient, aged 35, also had acetowhite lesion extended inside her cervical os (with positive ECC as HSIL later). However, since 2001, we have recommended not to do cryotherapy in such case. Four patients were hysterectomized because of having positive inner margins after LEEP or cancer except one patient, aged 33, with free margin after LEEP. Interestingly, there was a large LSIL patient, aged 31, in VIA-positive group who was also treated first with LEEP but the inner surgical ends were not free from tumor (but still LSIL). Therefore, she was also offered extrafascial total hysterectomy. Surprisingly, the final hysterectomy pathologic examination revealed residual HSIL inside her os. There was also one case of HPV infection, aged 35, who developed CIN I at 2 years later. This patient was treated by LEEP and both surgical margins turned out to be free from tumor.

We had followed up these 648 patients for 5 years (until October 2006) and found that no more cervical cancer cases developed. In summary, all of our volunteers are now free from cervical cancer.

Discussion

At this point of study, we could assess the findings of cervices at 1 year after cryotherapy done by 12 trained

Table 1. VIA test result versus colposcopic impression of all patients at 1 year after cryotherapy

	Colposcopic impression		
VIA test result	Abnormal	Normal	Total
Abnormal	35	7	42
Normal	142	464	606
Total	177	471	648

Table 2. VIA test result versus final histologic-confirmed diagnosis of 208 patients at 1 year after cryotherapy

VIA test result	Diagnosis							
	WNL	CVCT	SQM	PL	LSIL	HSIL	CA	Total
Abnormal	0	2	12	0	19	2	1	36
Normal	14	17	59	10	70	2	0	172
Total	14	19	71	10	89	4	1	208

WNL, within normal limit; CVCT, cervicitis; SQM, squamous metaplasia; PL, polyp; CA, cancer.

Thai nurses. It is noteworthy that for most of those treated (91.7%), the SCJ was still visible satisfactorily by the colposcopists at 1 year (Fig. 2). This is higher than satisfactory colposcopy rate of only 12.5% in 48 women with squamous cell carcinoma Pap results, mean age 50 years, examined by Charoenkwan *et al.*[12] and that of 50.9% in 106 women with any abnormal Pap results, mean age 44.7 years, examined by Chindavijak and Koralak[13]. Certainly, this is not because cryotherapy made the SCJ wider. The only reason might be our patients' younger age (mean 37.96, SD 4.47, range 31–46). As women get older, squamous metaplastic process of glandular epithelium bring the SCJ more inside. This explains why a woman aged above 45 years is not a proper client for VIA testing.

A belief about disadvantages of cryotherapy that after treatment, the SCJ recedes into the cervical canal, is no longer visible, and therefore is not able to serve any more as a landmark for detecting precancers was proposed because there was a study reported that cryotherapy could cause even cervical stenosis and hematometra in two of 67 women after treatment[14]. Likewise, if electrocautery was done near os after LEEP, it could result in unsatisfactory colposcopy rate of 76% (38/50 women) during follow-up visit, but if this was not done near os (2–3 mm away), unsatisfactory colposcopy rate would be lower to only 7.8% (2/49 women) ($P < 0.001$)[15], which is similar to our study. In our first study of its kind in parous women, most of the SCJs still seemed to be well out on the exocervix after it had healed postcryotherapy making repeat VIA assessment possible. This might be the result of using a shallow-cone cryotip, not a peaked tip into os, in our cryotherapy procedures. Therefore, it is likely that VIA will be an appropriate test for the follow-up of those previously treated patients. However, one case of VIA negative with SCJ absent but acetowhite lesion seen inside the os under colposcopy and then ECC turned out to be HSIL has given us the solid evidence supporting that our present dual-tract strategy (have to do Pap smear when SCJ cannot be totally seen) is appropriate[16].

No other evaluation of disease status other than VIA testing (such as colposcopy and/or biopsy) was obtained before treatment because we aimed to test the single-visit approach as it would probably be implemented as part of a cervical cancer prevention program. Therefore, actual treatment cure rates were not measurable. However, acetowhite lesions 1-year posttreatment provide an indication of the need for retreatment (and/or referral) and are something that can be feasibly monitored in regular programs, as part of routine quality assurance. Importantly, in this project, the test-abnormal rate at 1 year was only 6.5%, with one adenocarcinoma of low stage IA. The effectiveness of cryotherapy treatment originally performed as part of a SAFE demonstration project was difficult to evaluate because the only diagnosis on entry was VIA—no cytology, HPV testing, or any other method of quality control was obtained. However, the high disease negative rate of 85.5% (no HPV infection, no CIN, and no cancer) was achieved. This is comparable to its cure rate described in meta-analysis by Martin-Hirsch *et al.*[17].

These 12 nurses were trained in a 10-day VIA and Cryotherapy Clinical Skill Course of JHPIEGO[18] (Table 3). This competency-based humanistic training involves many clinical aspects such as pelvic examination skills, VIA testing skills, VIA image assessment skills, cryotherapy skills, counseling skills, infection prevention. During training, trainers usually emphasize that "small lesions are not significant." Colposcopy, certainly, could better detect smaller lesions. This is why colposcopy could still substantially detect LSIL cases in the VIA negative group. All of them were 70 cases of HPV infection and no CIN I was found. Fortunately, around 70% of HPV infection and CIN I (LSIL) could regress spontaneously within 2 years[19]. Because HSIL is usually large and larger than LSIL, it should be detected by VIA. Although cryotherapy was inappropriate if the adenocarcinoma was present but missed at initial testing, it could also be argued that a low stage of operable cancer was discovered as part of the project. Otherwise, it has very likely gone unreported or might be discovered only at a more advanced stage.

VIA's negative predictive value in primary testing is consistently reported at 96% or greater[20–22]. In this first secondary VIA testing study, likewise, high negative predictive values (99.7%) were still also found as mentioned above. Although positive predictive value was not measured in the primary testing of this study, a study using the same training method by the same group of trainers yielded this rate of 22.7%[23]. Predictably, there should be considerable overtreatment; however, cryotherapy is safe and has only minimal side effect. In addition, this single-visit approach was also proved to have highest cost effectiveness in cervical cancer prevention[24].

Our strength is that prospective postcryotherapy follow-up data collection in a large group of patients was done. However, before doing colposcopy, the colposcopists might check the latest result of VIA examination and, if positive, where the lesion was at that time on their own demand. Therefore, this was not an independent observation and could result in some bias.

Table 3. The 10-day VIA and Cryotherapy Clinical Skill Course schedule.

SVA USING VIA AND CRYTHERAPY CLINICAL SKILLS WORKSHOP (10 DAYS/20 SESSIONS)				
DAY 1	**DAY 2**	**DAY 3**	**DAY 4**	**DAY 5**
AM (4 hours) **Opening** • Welcome and introductions • Overview of the course (Goals, Objectives, Schedule) • Review course materials • Participant expectations • Precourse Questionnaire • Identify individual and group learning needs **Chapter 1: Introduction** • Background • Rationale for screening • Treatment • Managing precancerous disease • Links to other RH services	**AM (4 hours)** Agenda and opening activity **Recap: Chapter 1** **Chapter 2, 3: Human Papillomavirus (HPV), Cervix and Cervical Cancer** • Background **Activity**: Hand scratch game • The virus • How HPV induces cancer • Risk factors for cervical cancer **Activity**: Ball-of-Knowledge Game • Preventing cervical cancer	**AM (4 hours)** Agenda and opening activity **Recap: Chapter 2** **Chapter 2, 3: Pathophysiology of Cervical Cancer** • Key considerations for low-resource settings • Anatomy and physiology of normal cervix **Activity**: Small group work with flipcharts **Clinical Practice**: Observe and provide services in the clinic: • Counseling client • VIA • Cryotherapy	**AM (4 hours)** Agenda and opening activity **Recap: Chapter 3** **Role Play**: Counseling **Chapter 4: Talking with Women about Cervical Cancer** • Background • Clients' Rights • Confidentiality • Privacy • Who should talk with the woman • Being a good counselor **Clinical Practice**: Observe and provide services in the clinic: • Counseling clients • VIA • Cryotherapy	**AM (4 hours)** Agenda and opening activity **Recap: Chapter 4** **Role Play**: Counseling **Chapter 5: Preventing Infections in Healthcare Workers** • Disease transmission cycle • Essential IP practices **Clinical Practice**: Observe and provide services in the clinic: • Counseling clients • VIA • Cryotherapy
LUNCH	**LUNCH**	**LUNCH**	**LUNCH**	**LUNCH**
PM (3 Hours) **Precourse Skills Assessment** Assess each participant's skills: • Pelvic examination on models • Counseling (role play) **Discussion/Demonstration**: • Pelvic examination review • Demonstration on models **Activity**: • Pelvic examination practice **Review of day's activities**	**PM (3 Hours)** **Demonstration**: • Review of VIA and cryotherapy learning guide • VIA steps on model • Cryotherapy steps on model **Activity**: In groups of five, participants rotate as client (1), provider (1) and observers (3). • Pelvic examination • VIA test and Cryotherapy **Discussion**: Preparing for clinical work • Tour of clinic practice sites • Norms and conduct • Assignment to groups **Review of day's activities**	**PM (3 Hours)** **Review of Clinical Practice**: • Review cervical images • Discuss clinic observations • Additional practice on models as needed **Chapter 3: Pathophysiology of Cervical Cancer** (continued) • Appearance of the cervix in normal and abnormal states **Activity**: The VIA CD-ROM and identifying cervical conditions **Review of day's activities**	**PM (3 Hours)** **Review of Clinical Practice**: • Review cervical images • Discuss clinic observations • Additional practice on models as needed **Chapter 4: Talking with Women about Cervical Cancer** (continued) • Counseling prior to VIA testing • Counseling prior to cryotherapy • Counseling following cryotherapy • Questions frequently asked by women **Activity**: The VIA CD-ROM and identifying cervical conditions **Review of day's activities**	**PM (3 Hours)** **Review of Clinical Practice**: • Review cervical images • Discuss clinic observations • Additional practice on models as needed **Chapter 5: Preventing Infections in Healthcare Workers** (continued) • Hand Hygiene • Instrument processing • Storage • Safe workplace • Waste Disposal **Activity**: The VIA CD-ROM and identifying cervical conditions **Review of day's activities**

DAY 6	DAY 7	DAY 8	DAY 9	DAY 10
AM (4 hours) Agenda and opening activity **Recap: Week 1 Knowledge** **Role Play**: Counseling **Chapter 6: Client Assessment and VIA Testing** • Background • Who should be tested • When to perform VIA • Client Assessment • Instruments and supplies **Activity**: Olympics of Cryotherapy Setup **Clinical Practice**: Observe and provide services in the clinic: • Counseling clients • VIA • Cryotherapy	**AM (4 hours)** Agenda and opening activity **Recap**: Chapter 6 **Role Play**: Counseling **Chapter 7: Treatment and Followup** • Background • Outpatient treatment procedures • Cryotherapy treatment and referral **Clinical Practice**: Observe and provide services in the clinic: • Counseling clients • VIA • Cryotherapy	**AM (4 hours)** Agenda and opening activity **Recap**: Chapter 7 **Role Play**: Counseling **Activity**: • Midcourse Questionnaire • Review of questionnaire results **Clinical Practice**: Evaluate provision of services in the clinic: • Counseling clients • VIA • Cryotherapy	**AM (4 hours)** Agenda and opening activity **Role Play**: Counseling **Clinical Practice**: Evaluate provision of services in the clinic: • Counseling clients • VIA Cryotherapy **Review of Clinical Practice**: • Review cervical images • Discuss clinic observations • Additional practice on models as needed	**AM (4 hours)** Agenda and opening activity **Role Play**: Counseling **Clinical Practice**: Evaluate provision of services in the clinic: • Counseling clients • VIA Cryotherapy **Review of Clinical Practice**: • Review cervical images • Discuss clinic observations
LUNCH	**LUNCH**	**LUNCH**	**LUNCH**	**LUNCH**
PM (3 Hours) **Review of Clinical Practice**: • Review cervical images • Discuss clinic observations • Additional practice on models as needed **Activity**: Image Review **Activity**: Practice Exercises using Flash Card **Demonstration/Discussion**: • Maintenance and Care of Cryotherapy Unit **Review of day's activities**	**PM (3 Hours)** **Review of Clinical Practice**: • Review cervical images • Discuss clinic observations • Additional practice on models as needed **Chapter 7: Treatment and Followup** (continued) • Instruments and equipment • Cryotherapy procedure • Routine procedure **Activity**: Image Review **Activity**: Practice Exercises using Flash Card **Review of day's activities**	**PM (3 Hours)** **Review of Clinical Practice**: • Review cervical images • Discuss clinic observations • Additional practice on models as needed **Discussion**: Treatment and referral decision-making **Activity**: • Midcourse Image Assessment • Review of questionnaire results **Small Group Activity**: Review Facility Assessment and discuss next steps **Review of day's activities**	**PM (3 Hours)** **Discussion**: Preparing clinical site to provide VIA and cryotherapy services (continued): • Clinic setup • Client flow • Referral • Supervision • Implementation **Small Group Activity**: Develop Action Plans per facility group **Review of day's activities**	**PM (3 Hours)** **Course summary** **Course evaluation** **Closing ceremony**

Although we lost 56 VIA-negative volunteers to be referred, these numbers were only 8% of 704 women.

Since 2002, Thailand has implemented the dual-tract cervical cancer screening program which combined VIA (for age group of 30–45 years and SCJ could be seen) in conjunction with cryotherapy as a single visit, if feasible, and Pap smear (for other group of women) in remote area up to 13 from 76 provinces now[16]. Literature has also been reinforcing the need of adjunctive tests to cytology on screening for cervical cancer because of its low sensitivity (43.3%[25], 41%[26], 51%[27], 68.1%[28], 43%[29]) and to avoid multiple visits and delay between diagnosis and treatment. Therefore, we chose the VIA and cryotherapy single-visit program as an alternative to solve this problem. VIA is a low-cost test with an immediate result. It can be used in combination with cryotherapy to close the circle of prevention (not just screening) in settings where there are no effective laboratory facilities or no effective referral system for patients to have further diagnostic and treatment procedures by physicians such as colposcopy, biopsy, or LEEP, as in the present study. However, confirmed by this study and many recent studies, the specificity of this test is generally moderate (sensitivity 29–95% and specificity 49–91%)[30].

This study provides strong evidences supporting what our VIA nurse providers have done and have been doing in 13 of 76 provinces in Thailand now. Also, Thailand's implementation of the dual-tract strategy are supported by these data that we are going on the right way to prevent new cases of cervical cancer and unnecessary deaths in Thai women. Doing VIA and immediate cryotherapy for the eligible woman in a single visit is doing what's best for low-resource setting.

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Research Publication by The Royal Thai College of Obstetricians and Gynecologists Residency Training Program, 1994-2003†

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Objective: *To evaluate the impact of the manuscript requirement policy on research publications from the Royal Thai College of Obstetricians and Gynecologists (RTCOG) residency training program.*
Material and Method: *Names and research titles of RTCOG residents from 1994 to 2003 were used to search for publications in the Medline system and Thai Index Medicus.*
Results: *There were 759 residents with 188 (24.8%) articles published. The publications per year varied from 4.8% to 17.0%. Residents were the first authors of 75 articles (39.9%). One hundred and thirteen articles (60.11%) were published in local medical journals. The majority of articles published in international journals (65.3%) were published in the Journal of the Medical Association of Thailand. After initiation of the publication promotion policy in 1999, the number of publications in which residents were not the first authors increased from 39.8% to 60.2%.*
Conclusion: *The manuscript requirement policy can maintain the research publication rate.*

Keywords: *Obstetrics residency, Publications, Research activities, The Royal Thai College of Obstetricians and Gynaecologists, Training programs*

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Research training was incorporated into the Obstetrics and Gynecology residency training program in Thailand more than 15 years ago. The objective of research training is to improve clinical reasoning and encourage lifelong learning[1,2]. Most research projects involve volunteers, patients, data, or patient specimens, so results should be reported to the public. Because volunteer subjects exposed themselves to risks by participating in clinical research, it would be unethical not to benefit the public by publishing the results of these research projects. Therefore, the Royal Thai College of Obstetricians and Gynecologists (RTCOG), who supervises the residency training program, encourages residents to publish the results of their research projects. In 1999, the RTCOG instituted the policy that all research reports should include a full research report plus a manuscript ready for submission to a specific journal. Furthermore, if the residents' manuscript was accepted for publication by peer reviewed journals, the full research report can be considered as having passed the research part of the training program. The aims of the present study were to assess a research publication situation by the RTCOG residency training program over the last 10 years and to determine the impact of the manuscript requirement policy.

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Material and Method

The Royal Thai College of Obstetricians and Gynecologists (RTCOG) resident training data from the period 1994 to 2003 were included. The data sources were retrospectively reviewed from a list of resident's names, a list of resident's research topics. Medline and Thai Index Medicus searches were conducted to identify publications from these residents' research projects. The numbers of residents by institutes, number of publications, journals in which papers were published, and name of the first author were analyzed. The data are shown as numbers and percentages.

Results

There were 759 residents from 16 institutes during the 10-year period of the present study, with 188 publications (24.8%) in local and international journals. The percentages of publications varied from 0 to 60.9%,

Table 1. Number of residents and publications by institute

Institute	No. of residents	No. of publication (%)
Siriraj Hospital	133	28 (21.05)
Rajavithi Hospital	107	21 (19.63)
King Chulalongkorn Memorial Hospital	92	20 (21.74)
Chiang Mai University	79	23 (29.11)
Ramathibodi Hospital	71	12 (16.90)
Khon Kaen University	55	19 (34.55)
Vajira Hospital	55	19 (34.55)
Prince of Songkla University	44	14 (31.81)
Pramongkutklao Hospital	41	1 (2.44)
Bhumibol Adulyadej Hospital	34	14 (41.18)
Chonburi Hospital	23	14 (60.87)
Khon Kaen Hospital	8	2 (25.00)
Maharat Nakhon Rajasima Hospital	6	0 (0.00)
Hadyai Regional Hospital	4	0 (0.00)
Prapokklao Hospital	4	0 (0.00)
Supprasitthiprasong Hospital	3	1 (33.33)
Total	759	188 (24.77)
Range	3-133	0-28
Median, Mean	79	

Table 2. Number of publications with residents as first author by institute

Institute	Frequency	Percent
Prince of Songkla University	14	18.7
Chonburi Hospital	14	18.7
Bhumibol Adulyadej Hospital	13	17.3
King Chulalongkorn Memorial Hospital	10	13.3
Khon Kaen University	6	8.0
Ramathibodi Hospital	6	8.0
Chiang Mai University	4	5.3
Khon Kaen Hospital	2	2.7
Vajira Hospital	2	2.7
Pramongkutklao Hospital	1	1.3
Rajavithi Hospital	1	1.3
Siriraj Hospital	1	1.3
Supprasitthiprasong Hospital	1	1.3
Total	75	100
% of first authors	175/188 = 39.9	

Table 3. Number of publications with residents not as a first author by institute

Institute	Frequency	Percent
Siriraj Hospital	27	23.9
Rajavithi Hospital	20	17.7
Chiang Mai University	19	16.8
Vajira Hospital	17	15
Khon Kaen University	13	11.5
King Chulalongkorn Memorial Hospital	10	8.8
Ramathibodi Hospital	6	5.3
Bhumibol Adulyadej Hospital	1	0.9
Total	113	100
% of not first authors	113/188 = 60.1	

while the numbers of residents by institute varied from three to 133 (Table 1). Of the 188 publications found, residents were the first authors of 75 publications (39.9%), and not the first authors in 113 publications (60.1%) (Table 2, 3). The most popular journal (26%) was the Journal of the Medical Association of Thailand (JMAT), (Table 4). Seventy-two out of 75 publications (96%) in which the resident was the first author were published in a local journal (Table 5). Forty-two out of 113 publications (37.2%) in which residents were not the first author were published in the JMAT and 23 publications (20.3%) were published in international journals (Table 6). The number of residents per year varied from 56 to 87, with a mean of 75.9. The frequency and percentage of publications varied from 9 (4.8%) to 32 (17.0%), with a maximum of 32 publications in 1997 (Fig. 1). There were 51 (68%) publications with a resident as the first author from 1994 to1998, and 24 (32%) during 1999-2003 which peaked in 1997 (Fig. 2). Among publications in which the resident was not the first author, the number of publications was 45 (39.8%) during 1994-1998 and increased to 68 (60.2%) during 1999-2003 (Fig. 3).

Table 4. Total publications by journals

Journal	Frequency	Percent
J Med Assoc Thai	49	26.0
Vajira Med J	19	10.1
Siriraj Hosp Gaz	18	9.5
Chonburi Hosp J	14	7.4
R Thai Air Force Med Gaz	13	6.9
Songkla Med J	13	6.9
Srinagarind Med J	9	4.8
Bull Dept Med Serv	6	3.2
Int J Gynecol Obstet	6	3.2
Aust N Z J Obstet Gynaecol	15	2.7
J Obstet Gynaecol Res	5	2.7
J Rajavithi	5	2.7
Chula Med J	3	1.6
Khon Kaen Hosp Med J	3	1.6
Chiang Mai Med Bull	2	1.1
Contraception	2	1.1
J Clin Ultrasound	2	1.1
Obstet Gynecol	2	1.1
Ramathibodi Med J	2	1.1
Anticancer Res	1	0.5
Diabetologia	1	0.5
Eur J Obstet Gynecol Reprod Biol	1	0.5
J Obstet Gynaecol	1	0.5
Med J Srinakharinwirot	1	0.5
Med J Srisaket Surin Buriram Hosp	1	0.5
Med J Ubon Hosp	1	0.5
R Thai Army Med J	1	0.5
Thammasat Med J	1	0.5
Uttaradit Hosp Med Bull	1	0.5
Total	188	100

Discussion

The results show that, during the decade between 1994 and 2003, only 24.8% of research projects conducted in the RTCOG residency training program were published. Residents were the first author in 39.9% of these publications. After introducing the manuscript requirement policy in 1999, only the publications with a resident not as the first author had increased.

In both Europe and North America, it is thought that research training benefits residents, but methods and results of the training process need to be re-evaluated[2-5]. Residency training programs in most specialties have incorporated research training to improve scientific thinking and skills necessary to evaluate scientific publications[6,7]. Rivera et al reported

Table 5. Publication with residents as the first author by journals

Journal	Frequency	Percent
Chonburi Hosp J	14	18.7
R Thai Air Force Med Gaz	13	17.3
Songkla Med J	13	17.3
J Med Assoc Thai	7	9.3
Srinagarind Med J	5	6.6
Chula Med J	3	4.0
Khon Kaen Hosp Med J	3	4.0
Vajira Med J	3	4.0
Chiang Mai Med Bull	2	2.7
Ramathibodi Med J	2	2.7
Anticancer Res	1	1.3
Int J Gynecol Obstet	1	1.3
J Rajavithi	1	1.3
Med J Srinakharinwirot	1	1.3
Med J Srisaket Surin Buriram Hosp	1	1.3
Med J Ubon Hosp	1	1.3
Obstet Gynecol	1	1.3
R Thai Army Med J	1	1.3
Thammasat Med J	1	1.3
Uttaradit Hosp Med Bull	1	1.3
Total	75	100

Table 6. Publications with residents not as the first author by journals

Journal	Frequency	Percent
J Med Assoc Thai	42	37.2
Siriraj Hosp Gaz	18	15.9
Vajira Med J	16	14.2
Bull Dept Med Serv	6	5.3
J Obstet Gynaecol	6	5.3
Aust N Z J Obstet Gynaecol	5	4.4
Int J Gynecol Obstet	5	4.4
J Rajavithi Hosp	4	3.5
Srinagarind Med J	4	3.5
Contraception	2	1.8
J Clin Ultrasound	2	1.8
Diabetologia	1	0.9
Eur J Obstet Gynecol Reprod Biol	1	0.9
Obstet Gynecol	1	0.9
Total	113	100

Fig. 1 Number of publications by year 1994-2003

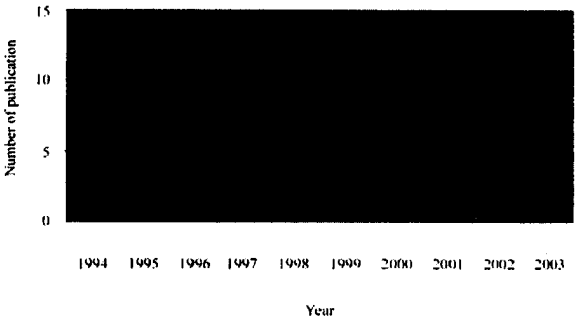

Fig. 2 Number of publications with resident as first author by year 1994-2003

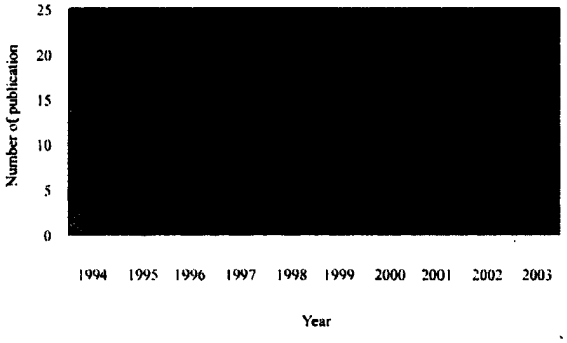

Fig. 3 Number of publications in which residents are not first author by year 1994-2003

that 69% of residents thought research should be a requirement for training, and the most common barrier to success of resident research was insufficient time[8]. Durning et al reported that a Resident Research Director increased the number of publications of the internal medicine residency training[9]. Obstetrics and Gynecology residency training in Thailand has included research training for a long time, but the present study

represents the first time that publication rates were evaluated.

The issue of who should be the first author is controversial. Some institutes have a very strict policy that only the residents should be the first author. Some institutes give their residents a period of six months to submit their manuscripts for publication. If their residents did not finish their manuscript within that period, faculty members who were their advisors are allowed to be the first author. Some institutes allow faculty members who were advisors of the research projects to be the first author. The justification for the last two policies was that most residents did not write manuscripts of their research work after they finished their training. The reasons for not writing manuscripts include; 1) residents were too exhausted from their intensive training, 2) residents did not know how to write manuscript for publishing in peer-reviewed journals, 3) papers published from residents' research work, even in the international journals, could not be used for their promotion in the future. The RTCOG executive committee realized and was concerned about the low publication rate from residents' research work. One potential strategy to increase the publication rate is to put manuscript writing as one of the requirements to complete residency training programs. This would also force advisors to train their residents on how to write a manuscript for publication in peer-reviewed journals. However, it was a surprise to see that after the manuscript requirement policy was introduced in 1999, the overall number of publications did not increase, only the number of publications with a resident not as the first author increased. The factors influencing publication rate of resident research should be further evaluated to improve the publication rate.

In conclusion, about a quarter of residents' research works were published. The manuscript requirement policy can maintain the number of publications from the Obstetrics and Gynecology residency training program and promote international publication. Other mechanisms are needed to increase both the rate of publication and number of publications in which residents are the first authors.

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การตีพิมพ์ผลงานวิจัยจากการฝึกอบรมแพทย์ประจำบ้านสูติศาสตร์และนรีเวชวิทยาระหว่างปีการศึกษา 2537-2546

หเทิญ ถิ่นธารา, ภิเศก ลุมพิกานนท์, แสงชัย พฤทธิพันธ์, เยื้อน ตันนิรันดร

วัตถุประสงค์: *เพื่อประเมินผลของนโยบายส่งเสริมการตีพิมพ์ผลงานวิจัยระหว่างการฝึกอบรมของแพทย์ประจำบ้านราชวิทยาลัยสูตินรีแพทย์แห่งประเทศไทย*

วัสดุและวิธีการ: *สืบค้นผลงานตีพิมพ์จากระบบ Medline และ Thai Index Medicus โดยใช้ชื่อของแพทย์ประจำบ้านหรือแพทย์ใช้ทุน และชื่องานวิจัยที่เสนอต่อคณะอนุกรรมการฝึกอบรมและสอบฯ ราชวิทยาลัยสูตินรีแพทย์แห่งประเทศไทย ระหว่างปีการศึกษา พ.ศ. 2537 - พ.ศ. 2546*

ผลการศึกษา: *มีแพทย์ประจำบ้านหรือแพทย์ใช้ทุนจำนวนทั้งสิ้น 759 คน มีผลงานตีพิมพ์ทั้งหมด 188 เรื่อง (ร้อยละ 24.8) อัตราการตีพิมพ์ผลงานวิจัยต่อปีอยู่ในช่วงร้อยละ 4.8 ถึงร้อยละ 17.0 มีแพทย์ประจำบ้านหรือแพทย์ใช้ทุนเป็นชื่อแรก 75 เรื่อง (ร้อยละ 39.9) ตีพิมพ์ในวารสารการแพทย์ท้องถิ่น 113 เรื่อง (ร้อยละ 60.11) ผลงานวิจัยที่ตีพิมพ์ในวารสารนานาชาติส่วนใหญ่ (ร้อยละ 65.3) ตีพิมพ์ในวารสารจดหมายเหตุทางแพทย์ หลังจากมีนโยบายส่งเสริมให้แพทย์ประจำบ้านหรือแพทย์ใช้ทุนส่งผลงานวิจัยตีพิมพ์เมื่อปีการศึกษา พ.ศ. 2542 พบว่าผลงานวิจัยตีพิมพ์ที่แพทย์ประจำบ้าน หรือแพทย์ใช้ทุนไม่ได้เป็นชื่อแรกเพิ่มขึ้นจากร้อยละ 39.8 เป็นร้อยละ 60.2*

สรุป: *นโยบายให้แพทย์ประจำบ้านหรือแพทย์ใช้ทุนเตรียมต้นฉบับพร้อมส่งตีพิมพ์ช่วยรักษาอัตราการตีพิมพ์ผลงานวิจัยระหว่างการฝึกอบรม*

Magnesium sulfate is not used for pre-eclampsia and eclampsia in Mexico and Thailand as much as it should be

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Objective In the past ten years effective treatments for pre-eclampsia and eclampsia have been evaluated and identified following large trials and systematic reviews. We investigated the extent of those effective interventions' implementation.
Methods Descriptive analysis of data collected as part of a cluster randomized trial. The trial was assigned the International Standardised Randomized Controlled Trial Number ISRCTN 14055385. Hospitals with more than 1000 deliveries per year not directly associated with an academic institution in Mexico City municipal area in Mexico ($n = 22$) and the north-east region of Thailand ($n = 18$) were included. All women delivering at the participating hospitals at two time periods in 2000 and 2002 contributed data on practice rates. The use of magnesium sulfate for pre-eclampsia and eclampsia were the outcomes.
Findings Eight out of 22 hospitals in Mexico (range 0.8% to 8.5%) and all 18 hospitals in Thailand (range 18.6% to 63.6%) used magnesium sulfate for women with pre-eclampsia. In Mexico, 11 of 22 hospitals used magnesium sulfate for eclampsia (range 9.1% to 60.0%). In Thailand, all 17 hospitals having eclampsia cases used magnesium sulfate (range 25% to 100%).
Conclusion Despite compelling evidence, magnesium sulfate use is below desired levels. Clinical practices should be audited and implementation of this effective intervention should be taken up as a priority where universal implementation is not in place.

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Une traduction en français de ce résumé figure à la fin de l'article. Al final del artículo se facilita una traducción al español. الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

Introduction

Pre-eclampsia is a multiple organ disorder of unknown etiology usually associated with raised blood pressure and proteinuria. Eclampsia, the occurrence of one or more convulsions (fits), is a rare but serious complication in patients with pre-eclampsia. Pre-eclampsia/eclampsia remains one of the leading problems that threaten safe motherhood, particularly in developing countries. It was estimated that hypertension complicates approximately 5% of all pregnancies and 11% of all first pregnancies.[1] Based on these estimations and case fatality rates, up to 40 000 women could die from pre-eclampsia and eclampsia each year.[1]

In a systematic review involving six trials (11 444 women) magnesium sulfate significantly reduced the risk of eclampsia (relative risk, RR 0.41; 95% confidence interval, CI: 0.29–0.58) and the risk of maternal death (RR 0.54; 95% CI: 0.26–1.10) among patients with pre-eclampsia although the latter was not statistically significant.[2,3] Magnesium sulfate was more effective than phenytoin for reducing the risk of eclampsia among patients with pre-eclampsia (two trials, 2241 women; RR 0.05; 95% CI: 0.00–0.84).[2]

Magnesium sulfate appears to be substantially more effective than phenytoin (six trials, 897 women)[4] or diazepam (seven trials, 1441 women)[5] for the treatment of eclampsia. Magnesium sulfate is therefore the anticonvulsant of choice for both prevention and treatment of eclampsia.[1]

Implementing magnesium sulfate for the prevention and treatment of eclampsia in low- and middle-income countries could potentially benefit hundreds of thousands of women.[6] This study aims to evaluate the use of magnesium sulfate for women with pre-eclampsia and eclampsia in Mexico and Thailand, where a cluster randomized trial to evaluate an educational strategy to change obstetric practices was conducted. The study methodology was published in detail elsewhere.[7] The main results related to the effects of the intervention was published separately.[8]

Methods

The study was conducted in two countries: the Mexico City municipal area, Mexico, and the north-east region of Thailand. Maternity units of hospitals with > 1000 deliveries/year that were not associated directly with a university or other academic/research department were eligible to participate. In Mexico, all state and social security hospitals in the Mexico City municipal area were approached. Twenty-two out of 34 hospitals approached were eligible and agreed to participate in the trial. In Thailand, 18 hospitals out of 19 in the north-east region agreed to participate. There were therefore 40 hospitals in this study. The objective of the main trial was to evaluate the improvement in obstetric practices using an active dissemination strategy to promote uptake of recommendations contained in the WHO Reproductive Health Library (RHL).[9]

A multifaceted intervention addressing potential barriers to evidence-based practice was conducted over a

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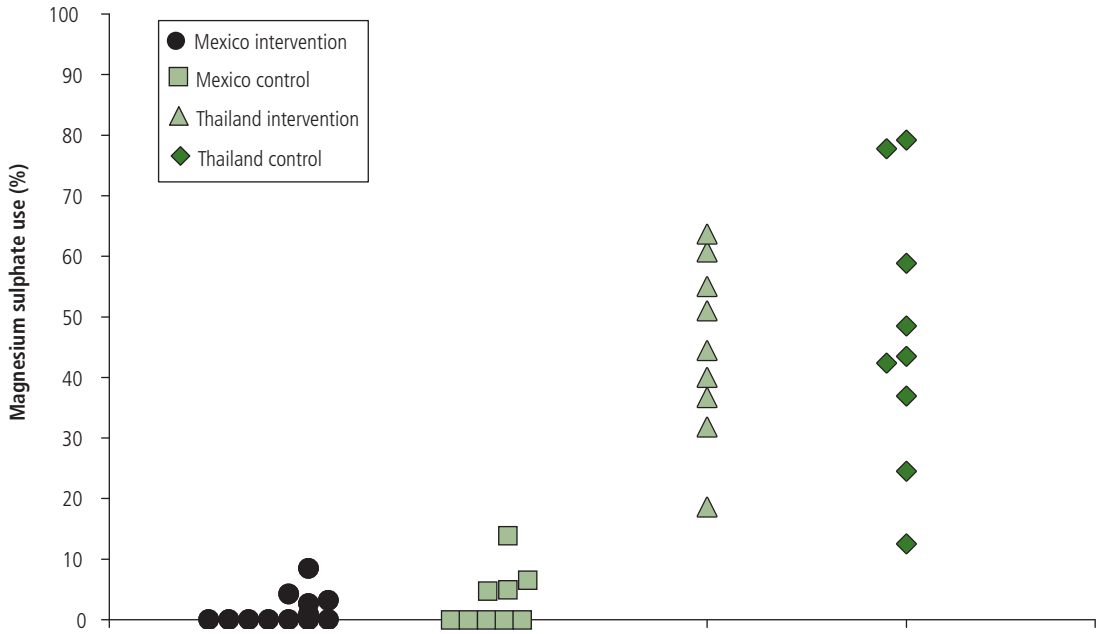
Fig. 1. **The rate of magnesium sulfate use for women with pre-eclampsia in Mexico and Thailand (some hospitals did not have any cases)**



period of six months following baseline data collection on clinical practices. Three interactive workshops focusing on principles of evidence-based medicine, the RHL and how to implement change formed the core intervention. The use of magnesium sulfate and other effective practices were not specifically addressed during the workshops.

The data on the occurrences of pre-eclampsia and eclampsia and the use of anticonvulsants were collected as part of measuring the rate of evidence-based practices in the main trial. The data were collected at baseline (September 2000) and 10 to 12 months after implementation of the intervention (September 2002). We collected data from 1000 women or for six months, whichever was reached first in each unit. Field workers not involved in the implementation of the trial collected the data. The data collection forms were completed in the postnatal wards mostly from hospital records. The mothers were consulted if information was missing from the records.

We report crude prevalence rates of pre-eclampsia and eclampsia. The rates of magnesium sulfate use and their 95% confidence intervals were considered at cluster (hospital) level.

The study 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 (HRP) and the ethics review committees of the participating institutions.

Results

The overall prevalence of pre-eclampsia in Mexico and Thailand was 5.5% (2320/41 828) and 1.9% (699/35 923), respectively. There was no statistically and clinically significant difference between the rate of magnesium sulfate use for women with pre-eclampsia (and eclampsia) at baseline and at the end of the study, in both intervention and control hospitals. We therefore combined the data collected during these two periods for each hospital. Only eight out of 22 hospitals in Mexico used magnesium sulfate for pre-eclampsia, and for those using magnesium sulfate the rate of use ranged from 0.8% (95% CI: 0–4.5) to 8.5% (95% CI: 4.8–13.6) among women with pre-eclampsia (Fig. 1). In Thailand, all 18 hospitals used magnesium sulfate for pre-eclampsia; the rates of use ranged from 18.6% (95% CI: 8.4–33.9) to 63.6% (95% CI: 50.9–75.1) in the intervention group and 12.5% (95% CI: 1.6–38.3) to 79.2% (95% CI: 65.0–89.5) in the control group (Fig. 1). In Mexico, phenytoin was more commonly used than magnesium sulfate but it was not used at all in Thailand. Diazepam was not used in either country for women with pre-eclampsia.

The overall prevalence of eclampsia was 0.6% (232/41 828) and 0.3% (122/35 923) in Mexico and Thailand, respectively. Only 11 out of 22 hospitals in Mexico used magnesium sulfate for eclampsia; for those using it the rates of use ranged from 9.1% (95% CI: 0.2–41.3) to 60.0% (95% CI: 14.7–94.7) in the intervention group and 3.8% (95% CI: 0.5–13.2) to 60.0% (95% CI: 14.7–94.7) in the control group (Fig. 2). In Thailand, there was one hospital that did not have patients with eclampsia at both baseline and at the end of the study; it was excluded from the analysis. The remaining 17 hospitals used magnesium sulfate for eclampsia. The rates of use ranged from 25.0% (95% CI: 0.6–80.6) to 100% (95% CI: 29.2–100) in the intervention group, and 25.0% (95% CI: 0.6–80.6) to 80.0% (95% CI: 44.4–97.5) in the control group (Fig. 2). Phenytoin was more commonly used than magnesium sulfate in Mexico but was not used at all in Thailand for eclampsia. Diazepam was rarely used in both countries.

Discussion

The prevalence of pre-eclampsia and eclampsia in Mexico was 5.5% and 0.6% respectively, which is quite similar to the overall global picture.[1] However, the corresponding rates in Thailand were 1.8% and 0.3%, which are lower. The uses of magnesium sulfate for pre-eclampsia and eclampsia were surprisingly low in Mexico. In Thailand, magnesium sulfate was used more frequently for both pre-eclampsia and eclampsia.

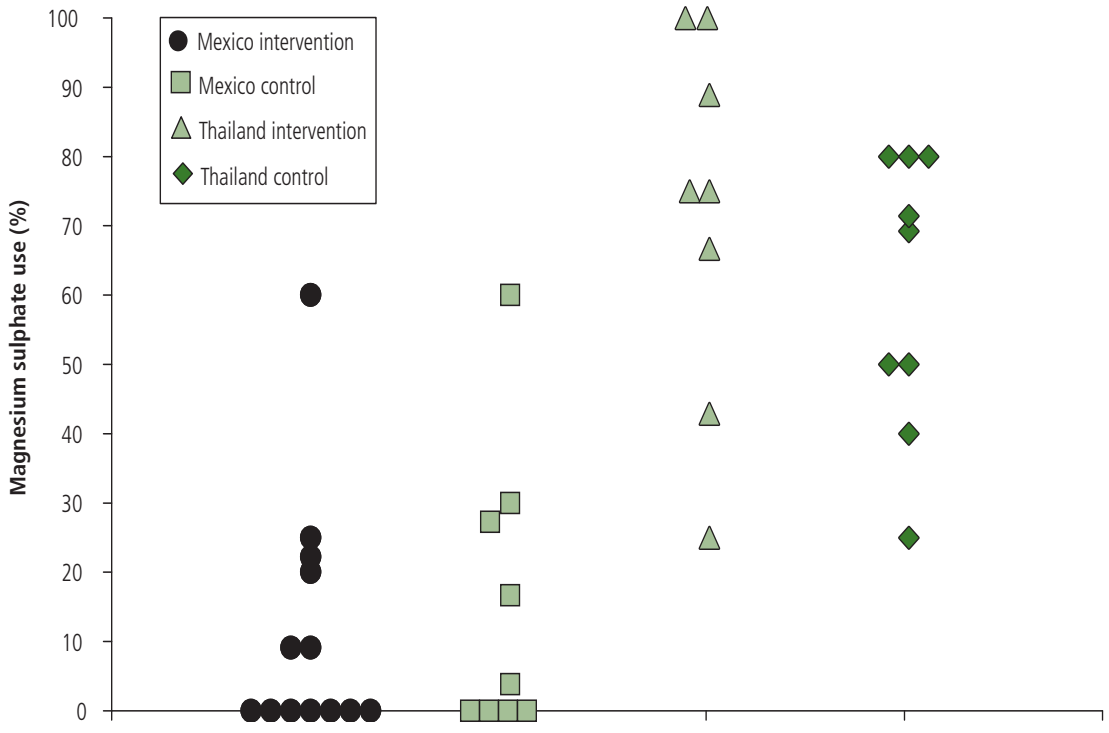
A report on the management of eclampsia from Sweden shows the remarkably increased use of magnesium sulfate: from 8% during 1980–1989 to 83% during 1990–1999.[10] A questionnaire survey of obstetricians in the United Kingdom and Ireland in 1996 indicated that 40% and 60% of respondents would use magnesium sulfate for pre-eclampsia and eclampsia, respectively.[11]

The very low rate of magnesium use particularly in Mexico is alarming. Magnesium sulfate is reasonably cheap and its effectiveness when used in pre-eclampsia and eclampsia has been clearly shown by evidence from randomized controlled trials and systematic reviews.[2,12,13] Although magnesium sulfate use for pre-eclampsia and eclampsia in Thailand is much higher than in Mexico, there is still room for improvement. Magnesium sulfate has been in the National Essential Drug List of Thailand since 1999. As of 2002, there were only 45 countries that had magnesium sulfate in their essential drug list (WHO unpublished data). As of 16 October 2006, the Mexican National Essential Drug List did not include magnesium sulfate (Edición 2005 del Cuadro Básico y Catálogo de Medicamentos, available at: http://www.salud.gob.mx). Responsible persons and organizations in these two countries should take immediate actions to ensure wider use of this effective and inexpensive drug for these conditions. Researchers and responsible persons in other low- to middle-income countries should also evaluate the situation regarding this issue and take appropriate actions.

Why has magnesium sulfate not become the treatment of choice particularly for eclampsia throughout the world? There are two possible hypotheses. First, magnesium sulfate is too cheap to motivate mass manufacturing, licensing, production and distribution. Second, health-care providers and administrators may be reluctant to adopt a practice that requires intensive monitoring for a condition (eclampsia) that is relatively infrequent.[14] Not having experience with magnesium sulfate administration has been proposed as a reason for not using it in the United Kingdom.[15] International organizations have advocated the use of magnesium sulfate in the treatment and prevention of eclampsia.[14] There are often systematic gaps between evidence of effectiveness and what is actually practiced. Failure in the registration, procurement and distribution mechanisms for magnesium sulfate contribute to its poor availability in Mozambique and Zimbabwe.[16] A survey of WHO drug information officers, regulatory officials and obstetricians in 12 countries was undertaken to identify barriers and facilitators to knowledge translation on the use of magnesium sulfate to treat pre-eclampsia. The perceived barriers include drug licensing and availability, inadequate and poorly implemented clinical guidelines, and the lack of political support for policy change.[17] There were significant regional and national differences in the importance of specific barriers.[17]

Our report is unique in that we measured actual practices of using magnesium sulfate in pre-eclampsia and eclampsia by extracting data from medical records of a large number of women from 22 hospitals in Mexico and 18 hospitals in Thailand. Based on anecdotal evidence before data collection, we had assumed that mag-

Fig. 2. **The rate of magnesium sulfate use for women with eclampsia in Mexico and Thailand (some hospitals did not have any cases)**



nesium sulfate would be routinely used in both Mexico and Thailand. For pre-eclampsia we anticipated some variation because the evidence was not strong at the time. The Magpie trial was published in June 2002.[18] However, the use of phenytoin for pre-eclampsia and eclampsia in Mexico was surprising. These data highlight the importance of collecting actual practice data rather than reported behaviour, which can often overestimate the quality of care.

Our data has the limitation of being retrospective. The quality of data might be somewhat limited to the standards of patient records in the two countries. However, both pre-eclampsia and eclampsia are serious conditions where women are hospitalized, and it is unlikely that magnesium sulfate would have been used but not recorded.

We conclude that magnesium sulfate is not as widely used for preventing and treating eclampsia as it should be, in spite of its inexpensiveness and the very clear evidence about its effectiveness. Immediate actions are necessary to promote its use in all countries around the world, including insertion in National Essential Drug Lists. Organizations, such as the International Federation of Gynecology and Obstetrics (FIGO) and the International Confederation of Midwives (ICM), their national counterparts and other professional organizations should advocate for the availability and use of magnesium sulfate, assist in the development of local treatment protocols to follow and training of health-care workers in the use of magnesium sulfate. Given the paucity of evidence to select appropriate strategies for implementation, research projects to evaluate innovative approaches to implement magnesium sulfate treatment are of high priority in low- and middle-income countries. ■

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Competing interests: None declared.

Résumé

Dans la municipalité de Mexico et en Thaïlande, le sulfate de magnésium n'est pas utilisé autant qu'il le devrait pour traiter les prééclampsies et les éclampsies

Objectif Au cours de la dernière décennie, des essais de grande ampleur et des revues systématiques de la littérature ont permis d'évaluer et d'identifier des traitements efficaces contre la prééclampsie et l'éclampsie. Nous avons examiné dans quelle mesure ces interventions efficaces étaient appliquées.

Méthodes Analyse descriptive des données recueillies dans le cadre d'un essai randomisé par grappes, ayant reçu le numéro d'essai contrôlé randomisé reconnu au plan international ISRCTN 14055385. Ont participé à l'étude les hôpitaux pratiquant plus de 1000 accouchements par an et non-associés directement à un établissement d'enseignement supérieur de la municipalité de Mexico (Mexique) (n = 22) et de la région nord-est de la Thaïlande (n = 18). Des données sur les fréquences de certaines pratiques ont été recueillies pour toutes les femmes ayant accouché dans les hôpitaux participant à l'étude pendant l'une des deux périodes étudiées, 2000 et 2002. L'étude visait à déterminer les taux d'utilisation du sulfate de magnésium contre la prééclampsie et l'éclampsie.

Résultats Huit des vingt-deux hôpitaux de Mexico (taux d'utilisation : 0,8 - 8,5 %) et la totalité des 18 hôpitaux thaïlandais (taux d'utilisation : 18,6 - 63,6 %) utilisaient du sulfate de magnésium pour traiter les femmes dans un état prééclamptique. Dans la municipalité de Mexico, 11 des 22 hôpitaux faisaient appel à ce produit contre l'éclampsie (taux d'utilisation : 9,1 - 60,0 %). En Thaïlande, la totalité des 17 hôpitaux accueillant des cas d'éclampsie ont utilisé du sulfate de magnésium (taux d'utilisation : 25 -100 %).

Conclusion Malgré les preuves éloquentes de son utilité, la fréquence d'administration du sulfate de magnésium est encore inférieure au niveau souhaitable. Une inspection des pratiques cliniques devrait être réalisée et la mise en œuvre de cette intervention efficace devrait être considérée comme une priorité partout où elle n'est pas universelle.

Resumen

El sulfato de magnesio se utiliza menos de lo necesario en los casos de preeclampsia y eclampsia en México y Tailandia

Objetivo En los últimos diez años se han evaluado e identificado los tratamientos más eficaces para la preeclampsia y la eclampsia mediante grandes ensayos y revisiones sistemáticas. Decidimos investigar el grado de aplicación de esas intervenciones eficaces.

Métodos Se llevó a cabo un análisis descriptivo de datos recopilados como parte de un ensayo aleatorizado por conglomerados. Se incluyeron en el ensayo -código ISRCTN (International Standardised Randomized Controlled Trial Number) 14055385- hospitales con más de 1000 partos al año no vinculados directamente a instituciones académicas situados en el término municipal de Ciudad de México (n = 22) y en el noreste de Tailandia (n = 18). Todas las mujeres que dieron a luz en los hospitales participantes en dos periodos de 2000 y 2002 aportaron datos sobre la atención recibida. Los resultados considerados fueron el uso de sulfato de magnesio contra la preeclampsia y contra la eclampsia.

Resultados Ocho de los 22 hospitales de México (intervalo: 0,8% - 8,5%) y los 18 hospitales de Tailandia (intervalo: 18,6% - 63,6%) trataron con sulfato de magnesio a las mujeres con preeclampsia. En México, 11 de los 22 hospitales utilizaron sulfato de magnesio contra la eclampsia (intervalo: 9,1% - 60,0%). En Tailandia, la totalidad de los 17 hospitales con casos de eclampsia administraron sulfato de magnesio (intervalo: 25% - 100%).

Conclusión Pese a lo contundente de la evidencia, el uso de sulfato de magnesio es inferior a lo deseable. Es necesario revisar la práctica clínica, y la aplicación de esta intervención eficaz debería considerarse una prioridad en los casos en que no se ha implantado de forma universal.

ملخص

نقص كمية سلفات المغنيزيوم المعطاة لمعالجة مقدِّمات الارتعاج والارتعاج في المكسيك وتايلاند

الغرض: تم في السنوات العشر الماضية تحديد وتقييم عمليات المعالجة الفعَّالة لمقدِّمات الارتعاج والارتعاج، بعد تجارب ودراسات منهجية موسَّعة. وقد استهدفت هذه الدراسة تقصِّي مدى تنفيذ تلك التدخلات الفعَّالة.

الطريقة: استُخدم في الدراسة التحليل الوصفي للبيانات التي جُمعت في إطار تجربة عنقودية معشاة. وقد أُعطي لهذه التجربة رقم ISRCTN14055385، وهو يمثِّل الرقم الدولي المعياري للتجارب المعشاة المضبطة بالشواهد. وقد شملت التجربة المستشفيات التي يزيد عدد الولادات التي تُجرى بها في كل عام على 1000 ولادة، والتي لا ترتبط مباشرةً بأي مؤسسة أكاديمية، وذلك في كلٍ من المنطقة البلدية لمدينة مكسيكوسيتي بالمكسيك (وعددها 22 مستشفى)، ومنطقة شمال شرقي تايلاند (وعددها 18 مستشفى). وقد قدَّمت جميع السيدات اللاتي ولدن في المستشفيات المشاركة في الدراسة في فترتَيْن زمنيَّتَيْن، هما عاما 2000 و2004، بيانات عن معدلات إعطاء سلفات المغنيزيوم. وكان معدل استخدام سلفات المغنيزيوم لمعالجة الارتعاج ومقدِّمات الارتعاج هو حصيلة البيانات.

الموجودات: تبيَّن أن 8 مستشفيات من جملة 22 مستشفى في المكسيك (بمجال يتراوح من 0.8% إلى 8.5%)، وأن جميع مستشفيات تايلاند البالغ عددها 18 مستشفى (بمجال يتراوح من 18.6% إلى 63.6%) قد أعطت سلفات المغنيزيوم للسيدات اللاتي عانين من مقدِّمات الارتعاج. وفي المكسيك، أعطى 11 مستشفى من جملة 22 مستشفى سلفات المغنيزيوم لمعالجة الارتعاج (بمجال يتراوح من 9.1% إلى 60%). وأما في تايلاند، فقد أعطت جميع المستشفيات التي واجهت حالات ارتعاج، والبالغ عددها 17 مستشفى، سلفات المغنيزيوم (بمجال يتراوح من 25% إلى 100%).

الاستنتاج: برغم البيِّنات القاطعة، لايزال استخدام سلفات المغنيزيوم دون المستويات المنشودة. وينبغي مراجعة الممارسات السريرية في هذا الشأن، وإعطاء أولوية لتنفيذ هذه الممارسة الفعَّالة في المناطق التي لا تنفَّذ فيها بشكل شامل.

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Prophylactic oral betamimetics for reducing preterm birth in women with a twin pregnancy (Review)

Yamasmit W, Chaithongwongwatthana S, Tolosa JE, Limpongsanurak S, Pereira L, Lumbiganon P

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Prophylactic oral betamimetics for reducing preterm birth in women with a twin pregnancy (Review)

Yamasmit W, Chaithongwongwatthana S, Tolosa JE, Limpongsanurak S, Pereira L, Lumbiganon P

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ABSTRACT

Background
Twin pregnancies are associated with a high risk of neonatal mortality and morbidity due to an increased rate of preterm birth. Betamimetics can decrease contraction frequency or delay preterm birth in singleton pregnancies by 24 to 48 hours. The efficacy of oral betamimetics in women with a twin pregnancy is unproven.

Objectives
To assess the effects of prophylactic oral betamimetics administered to women with twin pregnancies.

Search strategy
We searched the Cochrane Pregnancy and Childbirth Group Trials Register (May 2004), CENTRAL (*The Cochrane Library*, Issue 2, 2004), MEDLINE (January 1966 to May 2004), EMBASE (January 1985 to May 2004), and reference lists.

Selection criteria
Randomized controlled trials in twin pregnancies comparing oral betamimetics with placebo or any intervention with the specific aim of preventing preterm birth.

Data collection and analysis
Standard methods of The Cochrane Collaboration and the Cochrane Pregnancy and Childbirth Group were used. Trials were independently assessed for methodological quality by at least two authors, who extracted data using a data collection form.

Main results
Five trials (344 twin pregnancies) were included. All trials compared oral betamimetics to placebo. Betamimetics reduced the incidence of preterm labour (one trial, 50 twin pregnancies, relative risk (RR) 0.40; 95% confidence interval (CI) 0.19 to 0.86). However, betamimetics did not reduce preterm birth less than 37 weeks' gestation (four trials, 276 twin pregnancies, RR 0.85; 95% CI 0.65 to 1.10) or less than 34 weeks' gestation (one trial, 144 twin pregnancies, RR 0.47; 95% CI 0.15 to 1.50). Mean neonatal birthweight in the betamimetic group was significantly higher than in the placebo group (three trials, 478 neonates, weighted mean difference 111.2 grams; 95% CI 22.2 to 200.2). Nevertheless, there was no evidence of an effect of betamimetics in reduction of low birthweight (two trials, 366 neonates, RR 1.19; 95% CI 0.77 to 1.85) or small-for-gestational age neonates (two trials, 178 neonates, RR 0.92; 95% CI 0.52 to 1.65). Two trials (388 neonates) showed that betamimetics significantly reduced the incidence of respiratory distress syndrome but the difference was not significant when the analysis was adjusted for correlation of babies from twins. Three trials (452 neonates) showed no evidence of an effect of betamimetics in reducing neonatal mortality (RR 0.80; 95% CI 0.35 to 1.82).

Authors' conclusions
There is insufficient evidence to support or refute the use of prophylactic oral betamimetics for preventing preterm birth in women with a twin pregnancy.

PLAIN LANGUAGE SUMMARY

Not enough evidence to support or refute oral betamimetics (drugs to stop or prevent uterine contraction) for mothers for preventing preterm birth of twins

When babies are born too early they can suffer from ill health, which is sometimes severe and very occasionally babies die. This may be due to some of their organs not being mature enough, and their lungs, in particular, can struggle to support them. Twins are more likely to be born early and so suffer from these problems. Drugs that inhibit labour contractions (betamimetics) have been found to delay preterm birth in single babies. However, this review of trials found not enough evidence to support the routine use of oral betamimetics in preventing preterm birth in women with twin pregnancies.

BACKGROUND

The incidence of twins and higher order multiple pregnancy is increasing because of the wide availability of assisted reproductive technologies and accounts for 3% of all pregnancies (ACOG 1998). Twin pregnancies carry a higher risk of neonatal mortality and morbidity compared to singleton pregnancies. In the United States, neonatal mortality in twin pregnancies is 4.14% while it is 0.59% in singleton pregnancies (Powers 1994). These infants are at increased risk of neonatal death and long-term morbidity due to low birthweight, resulting from a combination of increased preterm birth and intrauterine growth restriction compared to singletons (Chitkara 2002).

Fifty per cent of twins are born preterm (WHO 2001). Twins are 5.4 times more likely to be born at less than 37 weeks of gestation compared with singletons and 8.2 times more likely to be born at less than 33 weeks of gestation (Alexander 1998). Problems related to preterm birth result in significant anxiety for the parents; in addition, these problems are also public health concerns because the premature babies need care with high cost and may have long-term disabilities. Preterm birth is associated with respiratory distress syndrome (a respiratory disorder that is characterized by failure of the immature lungs to expand and contract properly during breathing), intracranial haemorrhage (bleeding within the brain), necrotizing enterocolitis (a serious gastrointestinal disease in neonates characterized by mucosal or transmucosal necrosis of part of the intestine), bronchopulmonary dysplasia (a chronic lung condition that is caused by tissue damage to the lungs and usually occurs in immature infants who have received mechanical ventilation and supplemental oxygen) and cerebral palsy (a disability resulting from damage to the brain before, during, or shortly after birth and outwardly manifested by muscular incoordination and speech disturbances). Intrauterine growth restriction also affects twins more frequently than singletons and exerts a negative impact on survival of these babies (Branum 2003; Demissie 2002). In addition to increased perinatal mortality, perinatal morbidity is also more likely. A population-based, case-control study from Greece showed that when looking at a group of children with cerebral palsy and a group of non-cerebral palsy controls, twins were identified ten times more often in the group with cerebral palsy (odds ratio 10.2, $P < 0.05$) (Petridou 1996). In the United States, the incidence of severe handicap in babies of twin pregnancy is increased from 19.7 per 1000 babies of singleton pregnancy to 34.0 per 1000 babies of twin pregnancy (Luke 1992).

Reducing the rate of preterm birth in twins is a major goal of obstetricians worldwide. However, interventions to prevent preterm labour in twin pregnancies have been disappointing. Bed rest is the oldest proposed method for the prevention of preterm birth in twin pregnancies. A meta-analysis found not enough evidence to support a policy of routine hospitalization for bed rest in multiple pregnancy (Crowther 2001). Prophylactic cerclage has not been shown to be effective in routinely preventing preterm birth in twins (Papiernik 1998). Home uterine activity monitoring may possibly have a role in predicting preterm birth in very small and specific populations; however, a meta-analysis of six trials showed no significant benefit in preventing preterm birth in twin gestations (Colton 1995). Recent studies demonstrate the benefit of progesterone in reduction of preterm birth in a high-risk population for preterm birth; nevertheless, these trials recruited only singleton pregnancies (da Fonseca 2003; Meis 2003). Addition to intervention for reducing preterm birth, corticosteroids administration to mothers prior to preterm birth was shown to be effective in preventing respiratory distress syndrome and neonatal mortality (Crowley 1996).

Betamimetics can decrease contraction frequency or delay preterm birth by 24 to 48 hours (Gyetvai 1999). However, the effectiveness of these drugs in preventing preterm labour and preterm birth in twins is still unproven. Furthermore, betamimetics can cause maternal adverse effects from minor symptoms such as palpitations to life-threatening conditions such as pulmonary edema (Gyetvai 1999; Sciscione 2003) and have been associated with maternal death.

We conducted this review to evaluate the role of prophylactic oral betamimetics administered to women with a twin pregnancy for the prevention of preterm labour and preterm birth. The primary outcomes are the incidence of preterm labour, preterm birth, neonatal mortality, neonatal morbidity, and adverse maternal effects.

OBJECTIVES

To assess the effectiveness of prophylactic oral betamimetics for the prevention of preterm labour and birth for women with twin pregnancies.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomized controlled trials. Quasi-randomized controlled trials were not included.

Types of participants

All pregnant women carrying twins who did not show signs of preterm labour and had a gestational age between 20 weeks and 37 weeks.

Types of intervention

Oral betamimetic drugs (any dosage regimen, any agent) compared with placebo or any other intervention aimed at decreasing preterm labour and preterm birth.

Types of outcome measures

Pregnancy outcomes
(1) Spontaneous onset preterm labour (variously defined by authors);
(2) preterm prelabour rupture of membranes;
(3) preterm birth (less than 37 weeks' gestation);
(4) very preterm birth (less than 34 weeks' gestation);
(5) extremely preterm birth (less than 28 weeks' gestation).

Neonatal and infant outcomes
(1) Neonatal mortality;
(2) very low birthweight (less than 1500 grams);
(3) low birthweight (less than 2500 grams);
(4) small-for-gestational age (birthweight less than 10th centile);
(5) admission neonatal intensive care unit;
(6) use of mechanical ventilation;
(7) respiratory distress syndrome;
(8) intracranial haemorrhage (diagnosed by ultrasonography or postmortem);
(9) necrotizing enterocolitis;
(10) length of hospital stay;
(11) bronchopulmonary dysplasia;
(12) abnormal neurodevelopmental status at more than 12 months corrected age (developmental delay and/or cerebral palsy).

Adverse maternal effects
(1) Pulmonary oedema;
(2) cardiac arrhythmias;
(3) glucose intolerance;
(4) postpartum haemorrhage;
(5) maternal death;
(6) length of hospital stay.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

We searched the Cochrane Pregnancy and Childbirth Group trials register (May 2004).

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. monthly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness of a further 37 journals.

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 'Search strategies for identification of studies' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are given a code (or codes) depending on the topic. The codes are linked to review topics. The Trials Search Co-ordinator searches the register for each review using these codes rather than keywords.

In addition, we searched the Central Register of Controlled Trials (*The Cochrane Library* Issue 2, 2004) using the following search strategy.
#1 PREGNANCY-MULTIPLE*:ME
#2 TOCOLYTIC-AGENTS*:ME
#3 TOCOLYSIS*:ME
#4 TOCOLY*
#5 ((#2 or #3) or #4)
#6 (#1 and #5)

We also adapted the above search strategy to search MEDLINE (January 1966 to May 2004) and EMBASE (January 1985 to May 2004) by selecting appropriate MeSH and/or keywords from their respective thesauri.

No language restrictions were applied. Cited references from retrieved articles were searched for additional studies. Abstracts and letters to the editor were reviewed to identify randomized controlled trials that have not been published. If a randomized controlled trial was identified, the primary investigator was contacted directly to obtain further data. Editorials, indicating

expert opinion, were reviewed to identify and ensure that no key studies were missed for inclusion in this review.

METHODS OF THE REVIEW

Two authors screened the studies that were found as a result of the search strategy described earlier. All potential trials were selected for eligibility according to the criteria specified in the protocol using a standardized form. Trials that did not follow the criteria were excluded.

Trials under consideration were independently assessed for methodological quality by at least two authors. Any disagreements were resolved by discussion. We used standard criteria described in the Cochrane Reviewers' Handbook (Clarke 2003) to assess the trials.

Assessment of trial quality
Four major sources of potential bias and methods or avoidance of these biases were considered when assessing trial quality:
(1) selection bias - blinding of randomization;
(2) performance bias - blinding of intervention;
(3) attrition bias - completeness of follow up;
(4) detection bias - blinding of outcome assessment.

The quality assessment was based on a systematic assessment of the opportunity for each of these biases to arise.

A quality rating for blinding of randomization was assigned to each trial, using the criteria outlined in the Cochrane Reviewers' Handbook (Clarke 2003):
(A) adequate; (B) unclear; (C) inadequate; or (D) not used.

A quality rating of (A) yes; (B) cannot tell; or (C) no, was assigned to the other quality components (blinding of intervention, completeness of follow up and blinding of outcome assessment).

We assessed the quality of included studies by considering the major sources of bias (selection bias, performance bias, attrition bias, and detection bias). The trials that had not used allocation concealment and blinding of intervention or outcome assessment were excluded. Trials that had more than 20% loss of follow up for outcome measure also were excluded.

Data management and analysis
Data were extracted by the first and second authors using a data collection form. Where possible, data were extracted to allow an intention-to-treat analysis. We sought missing data from investigators of individual trials as necessary. The following data were extracted from each included study: (1) incidence of preterm labour and birth; (2) neonatal and infant outcomes; (3) adverse maternal effects; (4) extract whether steroids given routinely to all women; and, where recorded, the number and percentage of women given steroids in the intervention and control group. We explored steroid administration as a possible source of heterogeneity in subgroup analyses.

We expressed results as relative risks for dichotomous outcomes or weighted mean difference for continuous variables, and include 95% confidence intervals using the Review Manager software (RevMan 2002). We used the number of women as the denominator for incidence of preterm labour and birth and adverse maternal effects. For neonatal and infant outcomes, we used the number of babies as the denominator. To avoid incorrect conclusions due to the non-independence of babies from twin pregnancies, the sensitivity analysis was performed assuming a range of different degrees of correlation between twins. This was done by dividing both numerator and denominator by a range of numbers between 1 and 2. Dividing by 1 gave the unadjusted figures, assuming independence between twins, whereas dividing by 2 gave the most conservative figures, assuming complete correlation.

We conducted meta-analysis using the fixed-effect model. Heterogeneity was assessed using the I^2 statistic for heterogeneity. A value of more than 50% was interpreted as evidence of substantial heterogeneity. Where heterogeneity was found, we looked for an explanation. If studies with heterogeneous results were thought to be comparable, the statistical synthesis of the results was undertaken using a random-effects model.

Planned subgroup analyses included: (1) type of betamimetic agent; (2) dosage administered; (3) duration of therapy; (4) steroid administration; (5) setting (income-rich countries and income-poor/medium countries).

DESCRIPTION OF STUDIES

Eleven studies were identified as potentially eligible for inclusion in this review. Five trials were excluded. A further study is awaiting assessment, so this review includes five trials.

Excluded studies
See 'Characteristics of excluded studies' table.

Included studies
A total of 344 twin pregnant women participated in the five included studies comparing oral betamimetic agents with placebo (Ashworth 1990; Marivate 1977; Mathews 1967; O'Connor 1979; Skjaerris 1982). In one study (Mathews 1967) only the subset of trial participants who had a twin pregnancy (39 of 103 participants) was included.

Participants
Two trials (Ashworth 1990; Marivate 1977) were conducted in African countries while the others were conducted in Europe (Mathews 1967; O'Connor 1979; Skjaerris 1982). Mean age of participants, when described, was between 25.3 and 27.3 years. The gestational age at trial entry ranged from 20 weeks to 34 weeks. The mean gestational age at entry, when reported, was between 27.6 and 31.8 weeks. All trials except one (Mathews 1967)

described that cases with medical or obstetrical complications were excluded.

Interventions

All trials compared oral betamimetic agents with placebo, however, the types of betamimetic agents used in the trials were different (*see* 'Characteristics of included studies'). The betamimetic agents in the trials included salbutamol (Ashworth 1990), fenoterol (Marivate 1977), isoxuprine (Mathews 1967), ritodrine (O'Connor 1979), and terbutaline (Skjaerris 1982). All trials stopped the medication at 36 to 38 weeks of gestation or when labour started. The mean length of treatment, when reported, was between 32.6 and 63.4 days. None of the included trials described whether or not steroids were used for fetal lung maturity enhancement.

Outcomes

Only one study reported the incidence of preterm labour (Skjaerris 1982). All trials showed the incidence of preterm birth, but they used a different cutoff for gestational age. Three trials used 37 weeks' gestation as a cutoff, one used 36 weeks', and another used 38 weeks'. In addition, they used a different method for determining gestational age. Two studies used Dubowitz score (Marivate 1977; O'Connor 1979), one trial used certain last menstrual date or ultrasound (Ashworth 1990), and the remaining studies did not describe a specific method. There was also some inconsistency across trials with respect to the reporting methods of neonatal and maternal outcomes (*see* 'Characteristics of included studies').

METHODOLOGICAL QUALITY

The included trials were considered to be of reasonable quality. Allocation of concealment was reported in three trials (Ashworth 1990; Mathews 1967; O'Connor 1979). The remaining two trials did not describe the precise method of random allocation. All of the trials were double blind studies. Three of the trials had complete follow up (Marivate 1977; Mathews 1967; Skjaerris 1982). One study had a 10% loss to follow up rate (Ashworth 1990) that occurred more frequently in the betamimetic (10/80) than in the placebo group (6/80). Another study (O'Connor 1979) had no loss of follow up, but in 12.2% of all participants the neonates were not assessed for Dubowitz score (4/25 in the betamimetic group and 2/24 in the placebo group).

RESULTS

This review includes data from five trials with a total of 344 twin pregnancies. A total of 174 women were randomized to prescription of oral betamimetic agents and 170 women were randomized to placebo.

Pregnancy outcomes

(1) Spontaneous onset of preterm labour

Only one trial reported this outcome (Skjaerris 1982). The use of oral betamimetic agents resulted in a statistically significant decrease in the incidence of preterm labour (relative risk (RR) 0.40; 95% confidence interval (CI) 0.19 to 0.86).

(2) Preterm birth

Four trials reported the incidence of birth less than 37 weeks' gestation (Ashworth 1990; Mathews 1967; O'Connor 1979; Skjaerris 1982) and one trial reported the incidence of birth at less than 34 weeks' gestation (Ashworth 1990). The results showed no evidence of an effect of oral betamimetic agents in reduction of preterm birth less than 37 weeks' gestation (RR 0.85; 95% CI 0.65 to 1.10) or 34 weeks' gestation (RR 0.47; 95% CI 0.15 to 1.50). No significant heterogeneity was noted.

Neonatal and infant outcomes

(1) Neonatal mortality

This outcome was no mentioned in two trials. Three trials with a total of 452 neonates (Ashworth 1990; Mathews 1967; O'Connor 1979) showed no evidence of an effect of oral betamimetic agents in reduction of neonatal mortality (RR 0.80; 95% CI 0.35 to 1.82). No significant heterogeneity was noted. There is insufficient evidence to show difference between income-rich countries and income-poor/medium countries in term of effect on neonatal mortality.

(2) Very low birthweight, low birthweight and small-for-gestational age

No evidence of an effect of oral betamimetic agents in reduction of low birthweight (RR 1.19; 95% CI 0.77 to 1.85, Ashworth 1990; Mathews 1967) and small-for-gestational age (RR 0.92; 95% CI 0.52 to 1.65, Marivate 1977; O'Connor 1979) is noted. The results from three trials (Ashworth 1990; Marivate 1977; O'Connor 1979) show that mean birthweight in neonates whose mothers received oral betamimetics was significantly higher than in neonates whose mothers received placebo (weighted mean difference 111.2 grams; 95% CI 22.2 to 200.2).

(3) Respiratory distress syndrome

Two trials reported the incidence of respiratory distress syndrome in neonates (Ashworth 1990; Skjaerris 1982). In one trial, this outcome was defined as clinically significant if the baby required oxygen therapy from a headbox or ventilator, but in the other trial did not show how to diagnose this outcome. From these trials, neonates in the betamimetics group had a lower incidence of respiratory distress syndrome, compared to those in the placebo group (RR 0.30; 95% CI 0.12 to 0.77). However, if the analysis was adjusted for correlation of babies from twins, the difference between the groups was not significant (95% CI 0.11 to 1.16).

Adverse maternal effects

The only major adverse maternal effect that has been reported is a maternal death in one trial (RR 2.84; 95% CI 0.12 to 68.57, Ashworth 1990).

DISCUSSION

Although five trials included in this review were considered to be of reasonable quality, there were some limitations that should be considered in interpretation of the results.

Firstly, the allocation concealment was not clearly defined in two of the five trials. Of the other three trials with adequate allocation concealment, two trials had some participants, mostly in the betamimetic group, with incomplete outcome measurement.

Secondly, types and doses of betamimetics used in the trials varied. However, the dosage of each betamimetic used in these trials is comparable to dosage used in a singleton pregnancy (Anotayanonth 2004).

Thirdly, the outcomes reported in the trials were incomplete and variously defined. No trial reported on childhood outcomes.

Results of one study (Skjaerris 1982) suggested that betamimetics can reduce the rate of preterm labour, but this study has a very small sample size and there was not enough evidence that this intervention could reduce incidence of preterm birth. The difference in incidence of respiratory distress syndrome in neonates between the groups was not clear because the sensitivity analyses for different degrees of correlation between twins showed contrary results. The criteria used for diagnosis and assessment of severity of respiratory distress syndrome in various studies remains to be verified and the information as to whether there were any undisclosed co-interventions, such as steroid administration, needs to be ascertained. The neonates in the betamimetic group had a higher mean birthweight than in the placebo group, with a mean difference of 111.2 grams. The clinical relevance on childhood and later outcomes is uncertain. This finding was statistically significant, but has limited clinical importance as the mean birthweight of neonates in the placebo group was between 2360 and 2670 grams. More importantly, there were no demonstrated differences between neonates in the betamimetic and placebo groups in the incidence of low birthweight, small-for-gestational age and neonatal mortality.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence either supporting or refuting the use of prophylactic oral betamimetics for preventing preterm birth in women with a twin pregnancy.

Implications for research

There is still no effective intervention to prevent preterm birth in women with a twin pregnancy. Appropriate research is necessary for finding interventions that may be useful in these cases. Each of the included trials in this meta-analysis had a small sample size. If a trial is proposed to test the effect of betamimetics with a reduction rate of 50% of preterm birth (less than 34 weeks' gestation) at a 0.05 significance level and a power of 90%, a sample size of 524 twin pregnancies in each group is needed. In addition, the outcome measurements in such trial should include not only the incidence of preterm birth, but also the incidence of precisely defined immaturity-related neonatal morbidities and include longer term childhood outcomes.

POTENTIAL CONFLICT OF INTEREST

None known.

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TABLES

Characteristics of included studies

Study	Ashworth 1990
Methods	Blinding of intervention: yes. Blinding of outcome assessment: yes. Completeness of follow up: no.
Participants	Country: Zimbabwe. Number: 80 women in the intervention group and 80 women in the control group. Gestational age at trial entry: 24-32 weeks.
Interventions	Salbutamol 4 mg four times a day vs placebo.

Characteristics of included studies (*Continued*)

Outcomes	Incidence of - birth less than 37 weeks; - birth less than 32 weeks; - neonatal mortality; - birthweight less than 2500 grams; - respiratory distress syndrome; - maternal death. Mean birthweight.
Notes	
Allocation concealment	A – Adequate

Study	**Marivate 1977**
Methods	Blinding of intervention: yes. Blinding of outcome assessment: yes. Completeness of follow up: yes.
Participants	Country: South Africa. Number: 23 women in the intervention group and 23 women in the control group. Gestational age at trial entry: less than 33 weeks.
Interventions	Fenoterol 5 mg once a day vs placebo.
Outcomes	Incidence of - birth less than 38 weeks; - birthweight less than 10th centile. Mean birthweight.
Notes	
Allocation concealment	B – Unclear

Study	**Mathews 1967**
Methods	Blinding of intervention: yes. Blinding of outcome assessment: yes. Completeness of follow up: yes.
Participants	Country: England. Number: 20 women in the intervention group and 19 women in the control group. Gestational age at trial entry: 28-34 weeks.
Interventions	Isoxuprine 30 mg four times a day vs placebo.
Outcomes	Incidence of - birth less than 36 weeks; - neonatal mortality; - birthweight less than 2500 grams. Mean gestational age. Mean birthweight.
Notes	
Allocation concealment	A – Adequate

Study	**O'Connor 1979**
Methods	Blinding of intervention: yes. Blinding of outcome assessment: yes. Completeness of follow up: no.

Participants	Country: Ireland. Number: 25 women in the intervention group and 24 women in the control group. Gestational age at trial entry: 20-34 weeks.
Interventions	Ritodrine 10 mg every 6 hours vs placebo.
Outcomes	Incidence of - birth less than 37 weeks; - birth less than 32 weeks; - perinatal mortality; - birthweight less than 10th centile.
Notes	
Allocation concealment	A – Adequate

Study	**Skjaerris 1982**
Methods	Blinding of intervention: yes. Blinding of outcome assessment: yes. Completeness of follow up: yes.
Participants	Country: Sweden. Number: 25 women in the intervention group and 25 women in the control group. Gestational age at trial entry: 24-30 weeks.
Interventions	Terbutaline 5 mg three times a day vs placebo.
Outcomes	Incidence of - preterm labour; - birth less than 37 weeks; - birth less than 35 weeks; - respiratory distress syndrome.
Notes	
Allocation concealment	B – Unclear

vs: versus

Characteristics of excluded studies

Study	**Reason for exclusion**
Endl 1982	Trial tested the addition of a betamimetic agent to cervical cerclage.
Gummerus 1985	Trial of maintenance tocolytic therapy.
Gummerus 1987	Women eligible for trial entry included triplet pregnancies.
Keirse 1990	Trial of maintenance tocolytic therapy.
Melrose 1988	Trial tested the effects of routine hospitalization compared with selective hospitalization in women receiving ritodrine.

ANALYSES

Comparison 01. Oral betamimetic versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Preterm labour	1	50	Relative Risk (Fixed) 95% CI	0.40 [0.19, 0.86]
02 Preterm birth (less than 37 weeks' gestation)	4	276	Relative Risk (Fixed) 95% CI	0.85 [0.65, 1.10]
03 Very preterm birth (less than 34 weeks' gestation)	1	144	Relative Risk (Fixed) 95% CI	0.47 [0.15, 1.50]
04 Neonatal mortality			Relative Risk (Fixed) 95% CI	Subtotals only
05 Low birthweight (less than 2500 grams)			Relative Risk (Random) 95% CI	Subtotals only
06 Small for gestational age (birthweight less than 10th centile)			Relative Risk (Fixed) 95% CI	Subtotals only
07 Birthweight	3	478	Weighted Mean Difference (Fixed) 95% CI	111.22 [22.21, 200.24]
08 Respiratory distress syndrome			Relative Risk (Fixed) 95% CI	Subtotals only
09 Maternal death	1	144	Relative Risk (Fixed) 95% CI	2.84 [0.12, 68.57]
10 Neonatal mortality (subgroup analyses)	3	452	Relative Risk (Fixed) 95% CI	0.80 [0.35, 1.82]

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Gestational Age; Premature Birth [*prevention & control]; Tocolytic Agents [*administration & dosage]; *Twins

MeSH check words

Female; Humans; Pregnancy

COVER SHEET

Title Prophylactic oral betamimetics for reducing preterm birth in women with a twin pregnancy

Authors Yamasmit W, Chaithongwongwatthana S, Tolosa JE, Limpongsanurak S, Pereira L, Lumbiganon P

Contribution of author(s) Waralak Yamasmit designed the review, coordinated the authors, communicated with the editorial team, wrote the protocol, undertook independent quality assessments and data extraction, interpret data, and drafted the review.
Surasith Chaithongwongwatthana performed the literature searches, designed data collection form, undertook independent quality assessments and data extraction, entered data into RevMan, analysed and interpret data.
Jorge E Tolosa, Sompop Limpongsanurak, Pisake Lumbiganon, and Leonardo Pereira provided general and editorial advice on the drafts and approval of the version to be published.

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GRAPHS AND OTHER TABLES

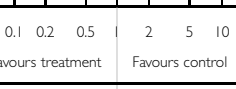
Analysis 01.01. Comparison 01 Oral betamimetic versus placebo, Outcome 01 Preterm labour

Review: Prophylactic oral betamimetics for reducing preterm birth in women with a twin pregnancy

Comparison: 01 Oral betamimetic versus placebo

Outcome: 01 Preterm labour

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Skjaerris 1982	6/25	15/25		100.0	0.40 [0.19, 0.86]
Total (95% CI)	25	25		100.0	0.40 [0.19, 0.86]
Total events: 6 (Treatment), 15 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.34 p=0.02					



Analysis 01.02. Comparison 01 Oral betamimetic versus placebo, Outcome 02 Preterm birth (less than 37 weeks' gestation)

Review: Prophylactic oral betamimetics for reducing preterm birth in women with a twin pregnancy

Comparison: 01 Oral betamimetic versus placebo

Outcome: 02 Preterm birth (less than 37 weeks' gestation)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Ashworth 1990	37/74	43/70		66.9	0.81 [0.61, 1.09]
Mathews 1967	6/20	2/19		3.1	2.85 [0.65, 12.42]
O'Connor 1979	7/21	10/22		14.8	0.73 [0.34, 1.57]
Skjaerris 1982	7/25	10/25		15.1	0.70 [0.32, 1.54]
Total (95% CI)	140	136		100.0	0.85 [0.65, 1.10]
Total events: 57 (Treatment), 65 (Control)					
Test for heterogeneity chi-square=3.05 df=3 p=0.38 I^2 =1.5%					
Test for overall effect z=1.25 p=0.2					

Analysis 01.03. Comparison 01 Oral betamimetic versus placebo, Outcome 03 Very preterm birth (less than 34 weeks' gestation)

Review: Prophylactic oral betamimetics for reducing preterm birth in women with a twin pregnancy

Comparison: 01 Oral betamimetic versus placebo

Outcome: 03 Very preterm birth (less than 34 weeks' gestation)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Ashworth 1990	4/74	8/70		100.0	0.47 [0.15, 1.50]
Total (95% CI)	74	70		100.0	0.47 [0.15, 1.50]
Total events: 4 (Treatment), 8 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.27 p=0.2					

Analysis 01.04. Comparison 01 Oral betamimetic versus placebo, Outcome 04 Neonatal mortality

Review: Prophylactic oral betamimetics for reducing preterm birth in women with a twin pregnancy

Comparison: 01 Oral betamimetic versus placebo

Outcome: 04 Neonatal mortality

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Assuming independence between twins					
Ashworth 1990	5/148	10/140		83.9	0.47 [0.17, 1.35]
Mathews 1967	4/40	0/38		4.2	8.56 [0.48, 153.83]
O'Connor 1979	0/42	1/44		12.0	0.35 [0.01, 8.33]
Subtotal (95% CI)	230	222		100.0	0.80 [0.35, 1.82]
Total events: 9 (Treatment), 11 (Control)					
Test for heterogeneity chi-square=3.81 df=2 p=0.15 I^2 =47.4%					
Test for overall effect z=0.54 p=0.6					
02 Assuming complete correlation between twins					
Ashworth 1990	3/74	5/70		72.2	0.57 [0.14, 2.29]
Mathews 1967	2/20	0/19		7.2	4.76 [0.24, 93.19]
O'Connor 1979	0/21	1/22		20.6	0.35 [0.01, 8.11]
Subtotal (95% CI)	115	111		100.0	0.82 [0.28, 2.40]
Total events: 5 (Treatment), 6 (Control)					
Test for heterogeneity chi-square=1.90 df=2 p=0.39 I^2 =0.0%					
Test for overall effect z=0.35 p=0.7					

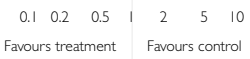
Analysis 01.05. Comparison 01 Oral betamimetic versus placebo, Outcome 05 Low birthweight (less than 2500 grams)

Review: Prophylactic oral betamimetics for reducing preterm birth in women with a twin pregnancy

Comparison: 01 Oral betamimetic versus placebo

Outcome: 05 Low birthweight (less than 2500 grams)

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Assuming independence between twins					
Ashworth 1990	80/148	74/140		67.6	1.02 [0.82, 1.27]
Mathews 1967	19/40	11/38		32.4	1.64 [0.90, 2.98]
Subtotal (95% CI)	188	178		100.0	1.19 [0.77, 1.85]
Total events: 99 (Treatment), 85 (Control)					
Test for heterogeneity chi-square=2.18 df=1 p=0.14 I^2 =54.2%					
Test for overall effect z=0.79 p=0.4					
02 Assuming complete correlation between twins					
Ashworth 1990	40/74	37/70		86.1	1.02 [0.75, 1.39]
Mathews 1967	10/20	6/19		13.9	1.58 [0.72, 3.50]
Subtotal (95% CI)	94	89		100.0	1.09 [0.81, 1.47]
Total events: 50 (Treatment), 43 (Control)					
Test for heterogeneity chi-square=1.03 df=1 p=0.31 I^2 =2.8%					
Test for overall effect z=0.55 p=0.6					

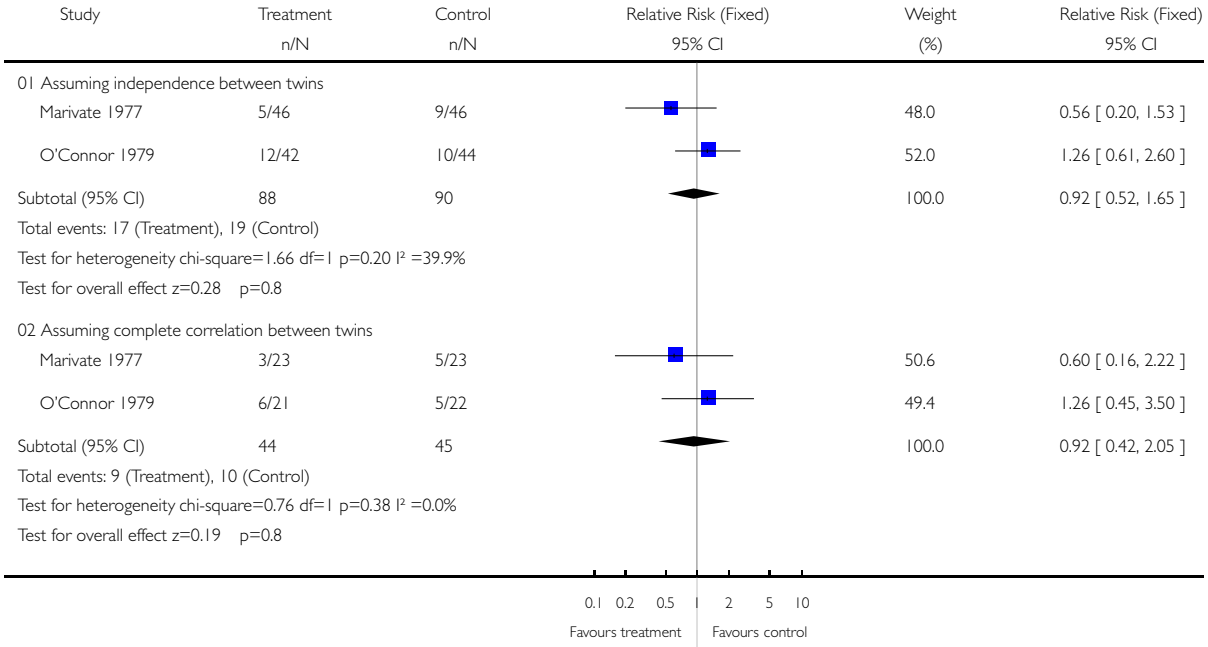


Analysis 01.06. Comparison 01 Oral betamimetic versus placebo, Outcome 06 Small for gestational age (birthweight less than 10th centile)

Review: Prophylactic oral betamimetics for reducing preterm birth in women with a twin pregnancy

Comparison: 01 Oral betamimetic versus placebo

Outcome: 06 Small for gestational age (birthweight less than 10th centile)

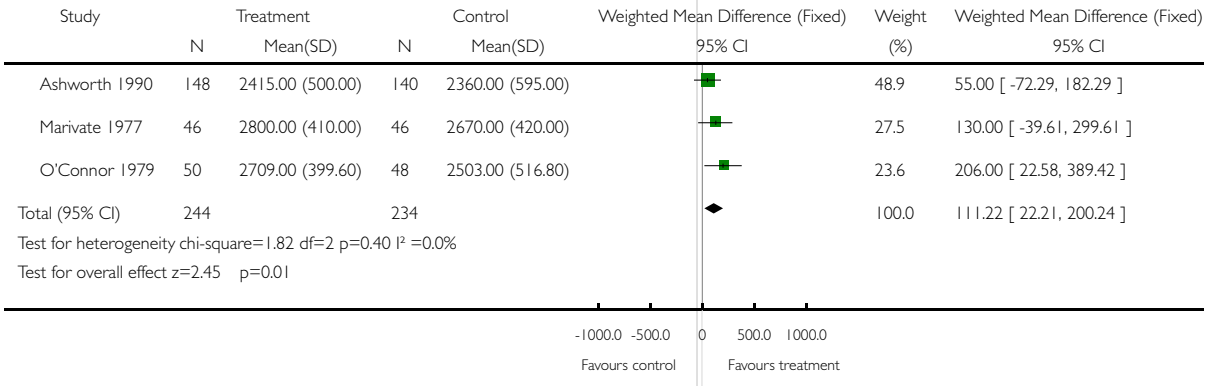


Analysis 01.07. Comparison 01 Oral betamimetic versus placebo, Outcome 07 Birthweight

Review: Prophylactic oral betamimetics for reducing preterm birth in women with a twin pregnancy

Comparison: 01 Oral betamimetic versus placebo

Outcome: 07 Birthweight

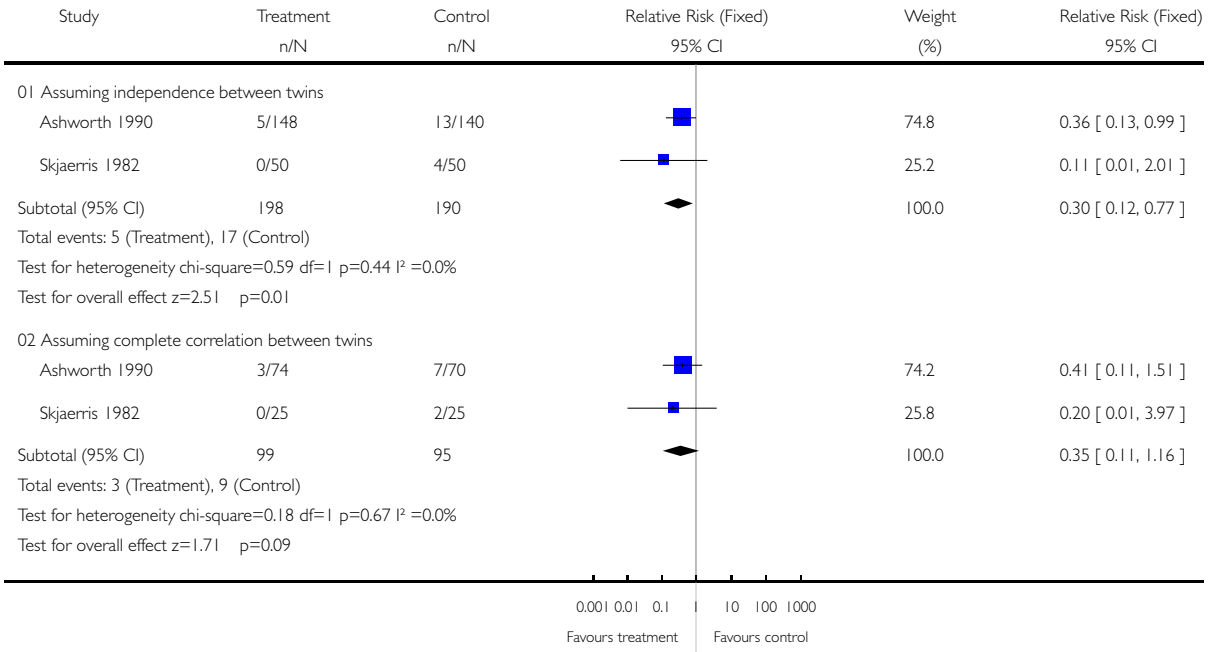


Analysis 01.08. Comparison 01 Oral betamimetic versus placebo, Outcome 08 Respiratory distress syndrome

Review: Prophylactic oral betamimetics for reducing preterm birth in women with a twin pregnancy

Comparison: 01 Oral betamimetic versus placebo

Outcome: 08 Respiratory distress syndrome

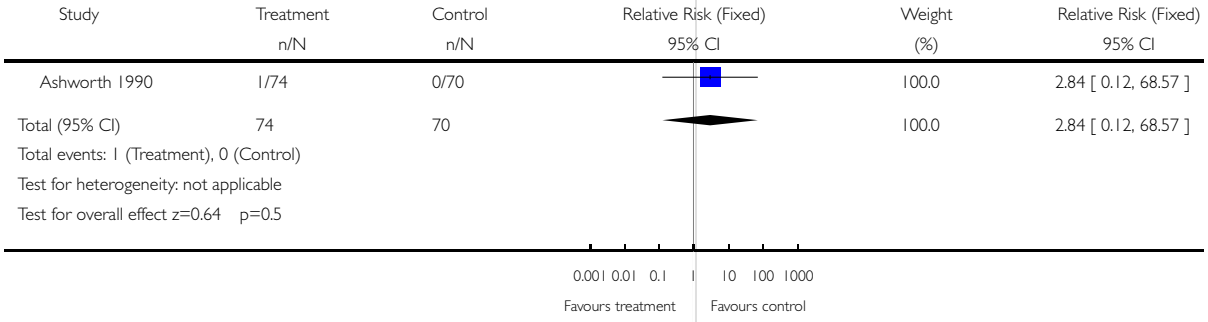


Analysis 01.09. Comparison 01 Oral betamimetic versus placebo, Outcome 09 Maternal death

Review: Prophylactic oral betamimetics for reducing preterm birth in women with a twin pregnancy

Comparison: 01 Oral betamimetic versus placebo

Outcome: 09 Maternal death



Analysis 01.10. Comparison 01 Oral betamimetic versus placebo, Outcome 10 Neonatal mortality (subgroup analyses)

Review: Prophylactic oral betamimetics for reducing preterm birth in women with a twin pregnancy

Comparison: 01 Oral betamimetic versus placebo

Outcome: 10 Neonatal mortality (subgroup analyses)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Income-rich countries					
Mathews 1967	4/40	0/38		4.2	8.56 [0.48, 153.83]
O'Connor 1979	0/42	1/44		12.0	0.35 [0.01, 8.33]
Subtotal (95% CI)	82	82		16.1	2.48 [0.48, 12.86]
Total events: 4 (Treatment), 1 (Control)					
Test for heterogeneity chi-square=2.17 df=1 p=0.14 I^2 =54.0%					
Test for overall effect z=1.08 p=0.3					
02 Income poor/medium countries					
Ashworth 1990	5/148	10/140		83.9	0.47 [0.17, 1.35]
Subtotal (95% CI)	148	140		83.9	0.47 [0.17, 1.35]
Total events: 5 (Treatment), 10 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.40 p=0.2					
Total (95% CI)	230	222		100.0	0.80 [0.35, 1.82]
Total events: 9 (Treatment), 11 (Control)					
Test for heterogeneity chi-square=3.81 df=2 p=0.15 I^2 =47.4%					
Test for overall effect z=0.54 p=0.6					

Antibiotic prophylaxis for fourth-degree perineal tear during vaginal birth (Review)

Buppasiri P, Lumbiganon P, Thinkhamrop J, Thinkhamrop B

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2007, Issue 4

http://www.thecochranelibrary.com

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Antibiotic prophylaxis for fourth-degree perineal tear during vaginal birth (Review)

Buppasiri P, Lumbiganon P, Thinkhamrop J, Thinkhamrop B

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ABSTRACT

Background
One to eight per cent of women suffer third-degree perineal tears (anal sphincter injury) and fourth-degree perineal tear (rectal mucosa injury) during vaginal birth, and these tears are more common after forceps delivery (28%) and midline episiotomies. Fourth-degree tears can become contaminated with bacteria from the rectum and this significantly increases in the chance of perineal wound infection. Prophylactic antibiotics might have a role in preventing this infection.

Objectives
To assess the effectiveness of antibiotic prophylaxis for reducing maternal morbidity and side-effects in fourth-degree perineal tear during vaginal birth.

Search strategy
We searched the Cochrane Pregnancy and Childbirth Group Trials Register (30 July 2005), the Cochrane Central Register of Controlled Trials (*The Cochrane Library*, Issue 2, 2005), MEDLINE (1966 to 15 July 2005), and LILACS (1982 to 15 July 2005).

Selection criteria
Randomised controlled trials which reported data comparing outcomes of prophylactic antibiotics versus placebo or no antibiotics in fourth-degree perineal tear during vaginal birth.

Data collection and analysis
No trials were found that met the selection criteria.

Main results
No randomised controlled trials were identified.

Authors' conclusions
There are insufficient data to support a policy of routine prophylactic antibiotics in fourth-degree perineal tear during vaginal birth. A well-designed randomised controlled trial is needed.

PLAIN LANGUAGE SUMMARY

No trials looking at routine antibiotics for women with severe perineal tears at birth

Most women are able to give birth without serious damage to their perineum. However, severe perineal trauma, which affects the muscle or tissue in the back passage, occurs in 1% to 8% of women giving birth and is common when forceps are used. There is an increased chance of infection when this happens, and antibiotics are often prescribed. The review of routine antibiotics for women with severe perineal tears found no trials. Hence, there is no strong evidence to support the effectiveness of prophylactic antibiotics in these situations. More research is needed.

BACKGROUND

Episiotomy is the incision in the perineal area to enlarge the vaginal orifice for easier vaginal birth. It consists of two types: midline or median and mediolateral style. Many studies have shown that routine episiotomy can cause such problems as persistent perineal pain, unsatisfied postpartum sexual function, and increasing anal sphincter injury leading to faecal or flatus incontinence (Christianson 2003; Jones 2000; Labrecque 1997; Nager 2001; Signorello 2001). Pain in this area can impact not only on a woman's daily activity but also on her relationship with her baby and her partner. A restrictive episiotomy policy (strict criteria to perform episiotomy only in proper cases such as short stature mother with short perineum, large size baby, or imminent severe laceration of perineum) has been in place for many years and is strongly supported by a Cochrane systematic review (Carroli 1999). In addition, prenatal perineal massage has also been introduced into practice to prevent perineal tears (Davidson 2000; Eason 2000; Johanson 2000; Labrecque 1999). One randomised controlled trial failed to show the effectiveness of perineal massage but concluded that it did no harm (Stamp 2001).

Most women are able to give birth without serious damage to the perineum, but 1% to 8% of women suffer severe perineal tears (anal sphincter injury with or without rectal mucosa injury) during vaginal birth (de Leeuw 2001; Riskin-Mashiah 2002; Samuelsson 2000; Samuelsson 2002; Sultan 1994). These tears are more common after operative vaginal birth, especially when forceps are used. The incidence of severe perineal lacerations after the use of forceps has been reported as 21% for third-degree and 7% for fourth-degree tears (Bofill 1996). Other risk factors include race (Asian women have the highest risk, perhaps due to small size mother and short perineum), midline episiotomy (short distance to anal sphincter), nulliparity (lesser elasticity than a multiparous mother), and high birthweight baby (de Leeuw 2001; Goldberg 2003; Homsi 1994; Jones 2000; Labrecque 1997; Nager 2001; Sultan 1994).

When a woman has a severe perineal tear during vaginal birth, there is thought to be an increased risk of infection. Laceration of the vagina and perineum during vaginal birth are classified as first, second, third and fourth degree. First-degree tears involve the vaginal mucosa and connective tissue. Second-degree tears involve the vaginal mucosa, connective tissue and underlying muscles. Third-degree tears involve a complete transection of anal sphincter and fourth-degree tears involve the rectal mucosa (Cunningham 2001; WHO 2003). When the rectal mucosa is ruptured, the wound is classified as contaminated (Waddell 1994) or clean-contaminated (Mangram 1999). Antibiotic prophylaxis is generally used where wounds have become, or are likely to become, contaminated, such as in colorectal surgery (Oates 1986; Song 1998). A Cochrane review has also shown antibiotic prophylaxis to be effective in reducing puerperal morbidity after cesarean section (Smaill 2002). On the other hand, a Cochrane review on antibiotic prophylaxis after operative vaginal birth could not conclude its effectiveness (Liabsuetrakul 2004).

A woman contracting infection after a severe perineal tear may also be at risk of other morbidities as a result of the tear, such as haematoma, dyspareunia, incontinence and recto-vaginal fistula (Crawford 1993; Homsi 1994; Labrecque 1997; Nager 2001; Signorello 2001; Sorensen 1988; Sultan 2002; WHO 2003).

While some authorities recommend that prophylactic antibiotics be used for severe perineal tears (WHO 2003), others have recommended against this course of action (Whitfield 1995). As widespread use of antibiotics may contribute to antibiotic-resistant bacteria (Towers 1998; Weinstein 1996), the over-use of antibiotics is being discouraged by many groups. However, antibiotic prophylaxis is a low-cost, accessible intervention which may prevent considerable maternal morbidity. It is therefore important to establish the benefits of prophylactic antibiotics for infection after severe perineal tears, and also to assess whether there are any adverse effects on mother or infant, by systematically reviewing the evidence.

OBJECTIVES

To assess the effectiveness of antibiotic prophylaxis for reducing maternal morbidity and side-effects in fourth-degree perineal tear during vaginal birth.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised controlled trials. Quasi-randomised controlled trial were not included.

Types of participants

Mothers with fourth-degree perineal tears as a result of vaginal birth.

Types of intervention

Antibiotic regimens used to prevent perineal wound infection compared either to placebo, or to no treatment, antibiotic treatment in women who get infection only, and comparisons between different antibiotic regimens.

Types of outcome measures

(a) Fever or puerperal febrile morbidity (body temperature of 38 ^{o}C or higher occurring on any two occasions in the first 10 days postpartum, exclusive of the first 24 hours);
(b) perineal wound infection (oedematous, erythematous, wound edge with pain, serosanguinous or frankly purulent material), or wound dehiscence (wound separation), recto-vaginal fistula (hole between the vagina and rectum);

(c) serious infectious complications such as bacteraemia, septic shock, septic thrombophlebitis, necrotising fasciitis, or death attributed to infection;
(d) pain (wound pain score or variously measured by authors);
(e) woman's comfort (unable to sit down or breastfeed) while in hospital and six weeks postpartum;
(f) length of hospital stay for mother;
(g) adverse reaction (such as allergic reaction, anaphylaxis, diarrhoea);
(h) maternal-infant interactions including breastfeeding;
(i) sexual function including dyspareunia (pain on sexual intercourse), sexual satisfaction, sexual sensation, time to resuming sexual intercourse;
(j) woman's satisfaction.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

We searched the Cochrane Pregnancy and Childbirth Group Trials Register by contacting the Trials Search Co-ordinator (30 July 2005).

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. monthly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness search of a further 37 journals.

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 'Search strategies for identification of studies' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are given a code (or codes) depending on the topic. The codes are linked to review topics. The Trials Search Co-ordinator searches the register for each review using these codes rather than keywords.

In addition, we searched CENTRAL (*The Cochrane Library,* Issue 2, 2005) using the following search strategy:

#1 PERINEUM single term (MeSH)
#2 perine*
#3 (tear* or injur* or lacerat* or trauma or damage*)
#4 (#2 and #3)
#5 (anal near sphincter) or (rectal mucosa) or rectum or (anal epithelium) or anus or (recto-vaginal fistulae) or (anorectal mucosa) or (anal skin)
#6 (tear* or injur* or damage* or lacerat* or rupture* or trauma)
#7 (#5 and #6)
#8 (obstetric* near tear*) or (obstetric near lacerat*)
#9 EPISIOTOMY single term (MeSH)
#10 episiotom* or postepisiotom*
#11 EXTRACTION OBSTETRICAL explode tree 1 (MeSH)
#12 vacuum or ventouse or forcep*
#13 deliver*
#14 (birth or childbirth or child-birth or (child next birth))
#15 antibio*
#16 ANTIBIOTICS explode all trees (MeSH)
#17 (#1 or #4 or #7 or #8)
#18 (#9 or #10 or #11 or #12 or #13 or #14)
#19 (#15 or #16)
#20 (#17 and #18 and #19)

We adapted this strategy to search MEDLINE (1966 to 15 July 2005), and LILACS (1982 to 15 July 2005). The title and abstracts of the retrieved articles were assessed and copies of relevant studies were collected. The references of retrieved articles were checked to locate other relevant trials.

We did not apply any language restrictions.

METHODS OF THE REVIEW

Four review authors undertook the review: three content experts and one biostatistician. One review author conducted the additional literature searches.

We planned to consider for inclusion all studies identified by the search strategy outlined above and to evaluate trials included for appropriateness and methodological quality without consideration of their results. Two review authors planned to assess trials for inclusion independently. We planned to resolve any differences of opinion by discussion. We planned to record and report in the review the reasons for excluding trials.

We planned to assess the methodological quality of the included studies using the criteria described in section six of the Cochrane Reviewers' Handbook (Alderson 2003).

Quality scores for allocation concealment were assigned to each trial, where A = adequate, B = unclear, C = clearly inadequate. We planned to eliminate studies when quality score was C.

Loss to follow up
We planned to assess studies for completeness of data collection, including differential withdrawal of participants or loss to follow up from different group:
(A) less than 3% of participants excluded;
(B) 3% to 9.9% of participants excluded;

(C) 10% to 19.9% of participants excluded;
(D) 20% or more excluded;
(E) unclear.

Blinding
Where appropriate, we planned to assess studies for blinding:
(A) blinding of participants;
(B) blinding of caregivers;
(C) blinding of outcome assessment;
(D) unclear;
(E) placebo used/not used due to the nature of the possible comparisons (i.e. alternative treatment rather than placebo).

Where feasible, we planned to undertake the following subgroup analysis:
(A) type of antibiotic regimen used.

We planned to extract and double-enter the data independently. There was no blinding of authorship. Whenever necessary, we planned to seek unpublished data from investigators. Statistical analyses would have been performed using the Review Manager software (RevMan 2003). We planned to process included trials data as described in the Cochrane Reviewers' Handbook (Alderson 2003).

We planned to compare dichotomous data using relative risks and 95% confidence intervals. Continuous data would have been compared, where possible, with weighted mean differences and 95% confidence intervals. Risk differences and numbers needed to treat would have been calculated where possible. Statistical heterogeneity between trials would have been assessed using the I^2 method described by Higgins 2002.

We planned to include all eligible trials in the initial analysis and to carry out analyses to evaluate the effect of trial quality. This would have been done by excluding trials given a C rating for quality of allocation concealment, then D and E for completeness of follow up, then D and E for blinding (where appropriate).

DESCRIPTION OF STUDIES

The search identified no randomised controlled trials, no observational studies and no case series.

METHODOLOGICAL QUALITY

Not applicable.

RESULTS

No randomised controlled trials were identified.

DISCUSSION

We did not identify any randomised controlled trials that compared the effectiveness of prophylactic antibiotic in fourth-degree tear during vaginal birth. No observational studies or case series to assess its effectiveness were identified either. Currently, prophylactic antibiotics are prescribed routinely in fourth-degree perineal tear during vaginal birth because they are usually cheap, easy to prescribe and trusted by doctors; but the harms of antibiotics include potential drug allergy, development of antibiotic-resistant bacteria and promotion of opportunistic infection.

AUTHORS' CONCLUSIONS

Implications for practice

Although restrictive use of episiotomy has been recommended for many years, it is still commonly performed. Fourth-degree perineal tear following an episiotomy is quite common. Prescribing antibiotics to mothers who have undergone episiotomy to prevent perineal wound infection is supported by expert opinion, but there are no data from randomised controlled trials or other types of studies to support their use.

Implications for research

Expert opinion gives limited insight into the potential benefits and harms of antibiotic prophylaxis for fourth-degree perineal tear during vaginal birth. Well-designed, multicentre, randomised controlled trials are needed to evaluate the effectiveness and adverse events of prophylactic antibiotics in fourth-degree perineal tear during vaginal birth.

POTENTIAL CONFLICT OF INTEREST

None known.

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INDEX TERMS

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Meditation therapy for anxiety disorders (Review)

Krisanaprakornkit T, Krisanaprakornkit W, Piyavhatkul N, Laopaiboon M

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Meditation therapy for anxiety disorders (Review)

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ABSTRACT

Background
Anxiety disorders are characterised by long term worry, tension, nervousness, fidgeting and symptoms of autonomic system hyperactivity. Meditation is an age-old self regulatory strategy which is gaining more interest in mental health and psychiatry. Meditation can reduce arousal state and may ameliorate anxiety symptoms in various anxiety conditions.

Objectives
To investigate the effectiveness of meditation therapy in treating anxiety disorders

Search strategy
Electronic databases searched include CCDANCTR-Studies and CCDANCTR-References, complementary and alternative medicine specific databases, Science Citation Index, Health Services/Technology Assessment Text database, and grey literature databases. Conference proceedings, book chapters and references were checked. Study authors and experts from religious/spiritual organisations were contacted.

Selection criteria
Types of studies: Randomised controlled trials.
Types of participants: patients with a diagnosis of anxiety disorders, with or without another comorbid psychiatric condition.
Types of interventions: concentrative meditation or mindfulness meditation.
Comparison conditions: one or combination of 1) pharmacological therapy 2) other psychological treatment 3) other methods of meditation 4) no intervention or waiting list.
Types of outcome: 1) improvement in clinical anxiety scale 2) improvement in anxiety level specified by triallists, or global improvement 3) acceptability of treatment, adverse effects 4) dropout.

Data collection and analysis
Data were independently extracted by two reviewers using a pre-designed data collection form. Any disagreements were discussed with a third reviewer, and the authors of the studies were contacted for further information.

Main results
Two randomised controlled studies were eligible for inclusion in the review. Both studies were of moderate quality and used active control comparisons (another type of meditation, relaxation, biofeedback). Anti-anxiety drugs were used as standard treatment. The duration of trials ranged from 3 months (12 weeks) to 18 weeks. In one study transcendental meditation showed a reduction in anxiety symptoms and electromyography score comparable with electromyography-biofeedback and relaxation therapy. Another study compared Kundalini Yoga (KY), with Relaxation/Mindfulness Meditation. The Yale-Brown Obsessive Compulsive Scale showed no statistically significant difference between groups. The overall dropout rate in both studies was high (33-44%). Neither study reported on adverse effects of meditation.

Authors' conclusions
The small number of studies included in this review do not permit any conclusions to be drawn on the effectiveness of meditation therapy for anxiety disorders. Transcendental meditation is comparable with other kinds of relaxation therapies in reducing anxiety, and

Kundalini Yoga did not show significant effectiveness in treating obsessive-compulsive disorders compared with Relaxation/Meditation. Drop out rates appear to be high, and adverse effects of meditation have not been reported. More trials are needed.

PLAIN LANGUAGE SUMMARY

Although meditation therapy is widely used in many anxiety-related conditions there is still a lack of studies in anxiety disorder patients. The small number of studies included in this review do not permit any conclusions to be drawn on the effectiveness of meditation therapy for anxiety disorders. Transcendental meditation is comparable with other kinds of relaxation therapies in reducing anxiety, and Kundalini Yoga did not show significant effectiveness in treating obsessive-compulsive disorders compared with Relaxation/Meditation. Drop out rates appear to be high, and adverse effects of meditation have not been reported. More trials are needed.

BACKGROUND

Anxiety disorder is a state of pathological anxiety which is characterized by autonomy (spontaneous occurred or minimal trigger by stimuli, tension and autonomic nervous system overactivity), intensity (in which the severity exceeds the individual's capacity to bear the level of intensity), duration, which is usually persistent or chronic, and behaviour, in which coping ability is impaired, with disabling behaviour as a consequence. According to Diagnostic and Statistical Manual of Mental Disorders 4^{th} edition (DSM-IV), anxiety disorders are classified into many types, including panic disorder, specific phobia, social phobia, obsessive-compulsive disorder(OCD), post-traumatic stress disorder(PTSD), acute stress disorder and generalised anxiety disorders (APA 1994).

Anxiety disorders are among the most prevalent psychiatric conditions in most populations studied. Studies have persistently shown that they produce inordinate morbidity, utilization of health care services, and functional impairment. Recent studies also suggest that chronic anxiety disorder may increase the rate of cardiovascular-related mortality (Horwath 2000). Two major studies in the United States have estimated the prevalence rates for a variety of anxiety disorders (the Epidemiological Catchment Area (ECA) study and the National Comorbidity Survey (NCS) study). The estimated lifetime prevalence rates for individual anxiety disorders are panic disorder (2.3-2.7%), generalized anxiety disorder (4.1-6.6%), OCD (2.3-2.6%), PTSD (1-9.3%), and social phobia (2.6-13.3%) (Blazer 1991, Kessler 1994, Eaton 1994, Kessler 1995). The prevalence of specific anxiety disorders appears to vary between countries and cultures. The lifetime prevalence rates for panic disorder ranged from 1.4 per 100 in Edmonton, Alberta, to 2.9 per 100 in Florence, Italy, with the exception of Taiwan which is 0.4 per 100 (Weissman 1997).

The debate over the primacy of biological or psychological factors in the pathophysiology of anxiety is gradually being replaced by a pragmatic approach based on research on the relative contributions of both. A parallel, unbiased approach in treatment research has begun to examine the merits of combined somatic and psychological treatments in anxiety. There has been tremendous progress in the nonpharmacologic treatment of anxiety disorders (Barrows 2002). Cognitive-behavioural therapies reflect a recent integration of the cognitive theories and methods invented by Aaron T. Beck and Albert Ellis, and behavioural theory based on the work of B.F.Skinner and Ivan Pavlov (Sadock 2003). Relaxation therapy is a behavioural approach which emphasises the development of a relaxation response to counteract the stress response of anxiety. Meditation is sometimes considered to be a form of relaxation therapy, however meditation not only creates a relaxation response but also produces an altered state of consciousness which facilitates the meta-cognitive mode of thinking which make possible the expectation of cognitive-behavioural benefits.

Growing scientific evidence, clinical experience and community attitudes are encouraging a shift to more natural and holistic forms of therapy as alternatives or adjuncts to pharmacological approaches in a variety of conditions. Meditation has a wide range of applications, but it is especially useful in treating stress and related disorders. Meditation is easily adapted to the general medical setting by adequately trained practitioners who have first hand experience of this form of therapy (Hassed 1996). A Psychologically-oriented definition by John V. Davis states that "Meditation is a set of attentional practices leading to an altered state or trait of consciousness characterized by expanded awareness, greater presence, and a more integrated sense of self" (Davis 1998). Meditation originated long ago before the advent of contemporary psychology. It originated in ancient India more than 3000 years ago and has existed in the ritual practice of some major religions and in many secular organisations. There are two general types of meditation: concentrative meditation and mindfulness meditation (Barrows 2002). Concentrative meditation is best represented in modern medicine by two programs, Transcendental Meditation (TM), which was introduced to the West during 1960s, and the relaxation response of Herbert Benson (Bensonian meditation) which was developed subsequently (Benson 1975). Concentrative meditation emphasises focusing the attention onto an object and sustaining attention until the mind achieves stillness. Relaxation and clarity of mind are the results of continuous practice.

Mindfulness meditation is another kind of meditation which emphasizes upon an open awareness to any contents of the mind that are emerging. After a period of practice, the patient will develop a sustainable attentive observational capability without reacting to their own thoughts and emotions. Mindful state with equanimity helps to retrain or decondition the previous pattern of reaction which is usually poorly adapted to external reality. It is represented by mindfulness-based stress reduction programs. The techniques of mindfulness meditation which focus on awareness to develop a detached observation of the contents of consciousness may represent a powerful cognitive behavioural coping strategy for transforming the ways in which we respond to life events (Astin 1997).

From preliminary review, Raskin conducted a controlled study comparing muscle biofeedback, transcendental mediation, and relaxation therapy. The study consisted of a six-week baseline period, six weeks of treatment, a six-week posttreatment observation period, and later follow-up (Raskin 1980). Kabat-Zinn conducted a study to determine the effectiveness of a group stress reduction program based on mindfulness meditation for patients with anxiety disorders. Patients were assessed using a structured clinical interview, and were found to meet the DSM-III-R criteria for generalized anxiety disorder or panic disorder with or without agoraphobia. They were trained in a Mindfulness-based stress reduction program and followed-up for 3 months (Kabat-Zinn 1992). Shannahoff-Khalsa reviewed two published clinical trials for treating obsessive-compulsive disorder(OCD) using a specific Kundalini Yoga protocol. This OCD protocol also included techniques that are useful for a wide range of anxiety disorders, as well as a technique specific for learning to manage fear, one for tranquillizing an angry mind, one for meeting mental challenges, and one for turning negative thoughts into positive thoughts (Shannahoff* 2004).

In terms of the adverse effects of meditation, Castillo reported that meditation can cause depersonalization and derealization (Castillo 1990), and there are several reports about the association between meditation and psychotic state (French 1975, Lazarus 1976, Walsh 1979, Chan-Ob 1999).

Though there is much research which has combined meditation therapy with conventional treatment in anxiety disorders, there is still a lack of reviews that provide substantial evidence on the effectiveness of meditation therapy programs, both for short-term and long-term effects and for acceptability in terms of practicality, feasibility, difficulty and concerns about the adverse effects.

OBJECTIVES

To investigate the effectiveness of meditation therapy programs (concentrative meditation and mindfulness meditation) which are specifically designed to treat anxiety disorders.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All relevant randomised controlled trials comparing meditation therapy alone or in combination with conventional treatment (consisting of drugs or other psychological treatment), or to another type of meditation or to conventional treatment alone or no intervention / waiting list control.

Exclusion: Open trials, case series, non-randomised controlled trials.

Types of participants

Inclusion criteria
Adults with a primary diagnosis of anxiety disorder (or corresponding to another diagnostic criteria including Diagnostic and Statistical of Mental disorders (DSM), International Classification of Disease -9(ICD-9) or ICD-10 clinical descriptions or research diagnostic criteria for neurotic disorders) with or without another comorbid psychiatric conditions, irrespective of gender, age, race or nationality.

Types of intervention

Operational definitions of meditation: The specific techniques of mind training which have two fundamental attentional strategies.
1. Concentrative meditation entails sustained attention directed toward a single object or point of focus. The aim is one-pointed attention to a single perception without distraction in order to produce the peaceful and one-mindedness state.
2. Mindfulness meditation (opening-up, insight meditation) involves the continual maintenance of a specific perceptual-cognitive set toward objects as they spontaneously arise in awareness with a nonreactive attitude. The salient features are full awareness or mindfulness of any contents of consciousness with equanimity.

Inclusion criteria
Meditation therapy, consisting of concentrative meditation, mindfulness meditation or combination of both.
For an intervention to be accepted as Meditation Therapy:
1. It must have been described in the trial report as: meditation, concentrative meditation, opening-up meditation, mindfulness meditation,insight meditation, mindfulness-based stress reduction program, Qiqong therapy, Pranayama (Hindu breathing meditation), Transcendental Meditation, Kundalini Yoga or Anapanasathi (Buddhist breathing meditation), Zen, ChunDoSupBup(Korean style meditation).
2. Meditation is the main intervention (in case of multi-component therapy).

Exclusion criteria
1) Meditation therapy that was not a well-organized program or was not specified to treat patients with anxiety disorders.

2) Meditation therapy that was a part of religious/ cult practice and was not specified to treat patients with anxiety disorders.

Comparison conditions: may be one or combination of
1) Pharmacological therapy: antianxiety agents mostly benzodiazepine compounds, antidepressants, adrenergic blocking agents etc.
2) Other psychological treatment : cognitive-behavioural therapy, insight-oriented psychotherapy, psychoanalysis , counseling etc.
3) Other methods of meditation.
4) No intervention or waiting list.

Types of outcome measures

Primary outcomes
1) Improvement in clinical scale of anxiety at the end of trial(continuous outcome):
Brief Outpatient Psychopathology Scale (Free 1977), Covi Anxiety Scale (Lipman 1976), Anxiety States Inventory (VanDercar 1980), Maudsley Obsessional-Compulsive Inventory (Rachman 1990), Hamilton Anxiety Rating Scale (Hamilton 1959), Yale-Brown Obsessive-Compulsive Scale (Goodman 1989), Symptom Checklist-90 (Derogatis 1973) etc.
2) Improvement in anxiety level specified by researcher or global improvement (categorical outcome: not improved, much improved or very much improved).

Secondary outcomes
1) Acceptability of treatment:
(a) any adverse effects that were reported in the trials.
(b) number of subjects who reported adverse effects.
2) Dropout (to be considered a proxy mesure of adherence to trial protocol).
3) Global impression of subjects to the program: Clinical Global Impression (CGI) (Guy 1970).
4) Number of experiences related to meditation (out of body, ecstatic feeling, depersonalisation, visual experience)

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

1. Electronic databases:

The following electronic databases were searched:
CCDANCTR-Studies was searched on 13-06-2005 using the following strategy:
Diagnosis = (Anxiety or Anxious or Agoraphobia or "Phobic Disorder*" or "Panic Disorder" or "Obsessive-Compulsive Disorder"or "Post-Traumatic Stress Disorders" or "Combat Disorder" or "War Neurosis" or "Acute Stress Disorder" or Neurosis or Neuroses or Neurotic)
and
Intervention = (meditation or "mindfulness-based stress reduction" or Vipassana or Zen or Yoga or yogic or Pranayama or Sudarshan or Kriya or Qi-gong or "Chi kung" or Kundalini or Chundosunbup)
and not
Diagnostic Criteria = "Not Stated" or None

CCDANCTR-References was searched on 13-06-2005 using the following strategy:
Keywords = (Anxiety or Anxious or Agoraphobia or "Phobic Disorder*" or "Panic Disorder" or "Obsessive-Compulsive Disorder" or "Post-Traumatic Stress Disorders" or "Combat Disorder" or "War Neurosis" or "Acute
Stress Disorder" or Neurosis or Neurotic)
and
Free-text = (meditation or "mindfulness-based stress reduction" or Vipassana or Zen or Yoga or yogic or Pranayama or Sudarshan or kriya or Qi-gong or "Chi kung" or Kundalini or Chundosunbup)

Complimentary and Alternative Medicine specific databases were searched:

CISCOM- Centralized Information Service for Complementary Medicine (CISCOM) to June 2005
System for Information on Grey Literature in Europe(SIGLE) search through June 2005
Terms used " Title= meditation AND title=anxiety", "Title= yoga AND Title = anxiety"

Health Services/Technology Assessment Text (HSTAT) database was searched.

2. Hand searching of specialist journals:
The main journals have been searched by Cochrane Schizophrenia Group (CSG) and Cochrane Depression, Anxiety and Neurosis Group, Trial Search Coordinator (CCDAN TSC).
Searching of conference proceeding of Anxiety Disorders Association of America 2003-4.
Search for the relevant studies cited in book chapters on the treatment of anxiety disorders.

3. Personal communication:

3.1 The authors of the included studies and experts in the fields were consulted to find out whether they know about any published or unpublished RCTs/ CCTs of meditation therapy and anxiety disorders, which have not yet been identified. Personal contact was made with persons whose work related to meditation. The list of personal contacts are shown in acknowledgement section.

3.2 Religious/spiritual organizations around the world (Internet web sites were extensively searched including Internet mailing lists) to find out whether they have conducted or know of the application of meditation in anxiety patients. Lists of organizations are shown in the acknowledgement section.

4. Search for ongoing trials:

metaRegister of Controlled Trials (mRCT) - active registers which comprised 13 clinical trial registries to June 2005.
HSR PROJECT (National Information Center on Health Services Research and Health Care Technology) to June 2005 .
National center for Complementary and Alternative Medicine under NIH .
National research register 2005 issue2.

5. Checking and follow searching from references found in 1-3. Science Citation Index of included and excluded studies were searched for further relevant studies.

METHODS OF THE REVIEW

Selection of studies
Two reviewers (KT and KW) screened the abstracts of all publications obtained by the search strategy. A distinction was made between:
1) Eligible studies in which meditation therapy alone or in combination was compared to a different type of psychological treatment, meditation or any active drugs.
2) Non-eligible studies in which meditation therapy was examined without a control element (open trial), non-randomised trials.

For articles that appeared to be eligible RCTs, the full articles were obtained and inspected to assess their relevance, based on the pre-planned criteria for inclusion.

Quality assessment
In order to ensure that variation was not caused by systematic errors in the design of a study, the methodological quality of the selected trials were assessed by two independent reviewers (KT and KW), using the criteria described in the Cochrane Handbook. The criteria are based on the evidence of a strong relationship between the potential for bias in the results and allocation concealment (Schulz 1995) and are defined below:

1. Were the inclusion and exclusion criteria clearly defined?
2. Was the allocation concealment properly done?
3. Were treatment programme, other than the interventions, identical?
4. Were important baseline characteristics reported and comparable?
5. Were the outcomes of patients who withdrew described and included in the analysis?
6. Were the outcome measures clearly defined, and valid?

Three quality categories were set:
High quality - all criteria met
Moderate quality - one or more criteria only partially met
Low quality - two or more criteria not met

According to The Cochrane Handbook for Systematic Reviews of Interventions , adequacy of allocation concealment was also judged (Higgins 2005).

A: Adequate
B: Unclear
C: Inadequate
D: Was not used

Data extraction and management
Data were independently extracted by two reviewers (KT and KW) using a predesigned data collection form. Any disagreements were discussed with a third reviewer (PN), the decisions documented and where necessary, the authors of the studies contacted to help resolve the issue. All exclusion/ drop outs were identified. In the case of trials using a crossover design, to exclude the potential additive effect in the second or more stages on these trials, only data from the first stage were analysed.

Data analysis

Dichotomous outcomes
Dichotomous outcomes were analysed by calculating the relative risk for each trial, with the precision in each result expressed using 95% confidence intervals. The relative risks from the individual trials were combined through meta-analysis if data available. When overall results were significant, the number needed to treat (NNT) was calculated (where no clinical, methodological or statistical heterogeneity was identified) by pooled analysis of the overall relative risk with an estimate of the event in the experimental group and control group of the trials.

Continuous outcomes
Data on continuous outcomes will be analysed in RevMan 4.2.7 (Review Manager 2004). Considering that the data using standardized mean difference are frequently skewed, the means not being the centre of the distribution. The statistics for meta-analysis are thought to be able to cope with some skew, but are formulated for parametric data. To avoid this potential pitfall the following standards were applied to all data before inclusion:
1. Standard deviations and means were reported or obtained from authors.
2. For data with finite limits, such as the endpoint scale data, the standard deviation (SD), when multiplied by 2, is less than the mean. Otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution (Altman 1996). The reviewers reported data that do not meet the first or second standard in the 'other data' tables.
For change data (endpoint minus baseline) in the absence of individual patient data, it is impossible to know if data are skewed. Where both change and endpoint data are available for the same outcome category, endpoint data only are presented. Authors of studies reporting change data only were contacted for endpoint figures. Non-normally distributed data were reported in the 'Other data types' tables.

Subgroup analysis

Due to clear differences in techniques and responses, rather than undertaking an overall pooled analysis, the data were analysed in subgroups according to the following categories:
1. type of meditation (concentrative or mindfulness meditation)
2. different type of anxiety disorders
Subgroup analyses would only be undertaken if a sufficient number of studies were identified.

Analysis of Heterogeneity
Heterogeneity can occur from many sources. An important aspect of every meta-analysis is to consider and emphasise the existence of heterogeneity and to take account of this in the interpretation of results. Sources of heterogeneity (clinical heterogeneity) can be divided in to two groups: biologic and methodologic .

Biological:
1. Characteristic of patients: age, socioeconomic status, education
2. Type of anxiety disorder: Generalised anxiety disorder, panic disorder, phobic disorder etc.
3. Disorder severity and chronicity: mild, moderate, severe

Methodological
1. Type of meditation
(a) Techniques: concentrative, mindfulness meditation or combination.
(b) Intensity of practice: daily, many times a day, duration of meditation per session.
2. Follow up period: at the end of trial or a period after trial.
3. Multi-component intervention: drugs, counseling, psychotherapy etc.

Strategies for exploring heterogeneity:
1. Identification of the methodological differences between studies.
2. Identification of the biological differences in study sample.
3. Subgroup analysis.
4. Meta-regression if enough data are available.

The test for homogeneity and I-square which provide an estimate of the percentage of variability due to heterogeneity were done using Review Manager 4.2.7
In case of homogeneity of studies result, the fixed effect model was used in meta-analysis.

Sensitivity analysis:
A sensitivity analysis was planned to test the robustness of effects of assumptions by examining the influence of the following on the results of the statistical analyses:
1. the effect of the quality criteria
2. comorbid depressive disorder
3. concomitant physical disorder
4. blinding of raters
The sensitivity analysis in this study was not done due to the paucity of eligible studies.

Publication bias
The funnel plot (Light 1984, Egger 1997) was planned to determine publication bias, by plotting the effect size against sample size. Publication bias may result when trials with negative results are not published.

DESCRIPTION OF STUDIES

At the preliminary phase of searching, 50 studies were found. The majority of these studies tested various meditation methods in anxiety subjects with a variety of anxiety conditions such as test anxiety, music performance anxiety, speech anxiety, complaints of anxiety , anxiety related to medical illnesses and psychoneuroses without any definite statement of diagnosis. Using the diagnostic criteria for psychiatric disorder (DSM or ICD classification) and limited to include only Randomised Controlled Trials, 46 studies were excluded from the early phase.

Two studies (Lu 1998; Sahasi 1989) were excluded from the reviews and put in the excluded studies section.
In Lu 1998 patients were diagnosed as having generalized anxiety disorder by a physician but no diagnostic criteria was stated. The selection of patients was done alternately (thus not a true randomisation technique). Sahasi 1989 used consultant psychiatrists to diagnose anxiety-neurotic patients on the basis of DSM-III. However the subject selection was not done using a true randomization method, it was by using an odd-even number and patients who were assigned to the yoga group were shifted to the drug group according to willingness of participants .

Raskin 1980 and Shannahoff* 1999 were the only 2 included studies according to the inclusion criteria.
Raskin(1980) compared 3 treatment modalities: Transcendental Meditation(TM), Electromyography-Feedback (EMG-FB) and Relaxation Therapy(RT).
Shannahoff* 1999 compared Kundalini Yoga with Mindfulness Meditation.

Design
Both studies were randomised controlled trials using active control comparisons (another type of meditation, relaxation, biofeedback). Antianxiety drugs were used as usual. No placebo or waiting list control were used. The duration of trials ranged from 3 months(12 weeks) in Shannahoff* 1999 to 18 weeks in Raskin 1980.

Settings
Both studies were conducted in United States of America. Using out-patient group setting, one group of participants in the Raskin 1980 study was sent to the Transcendental Meditation Centre and returned to have electromyographic measures at the study site.

Participants
In Raskin 1980 participants were diagnosed with anxiety neurosis according to DSM-II (1968) and the Taylor Manifest Anxiety

Score(TMAS) were at least 21(above 80 percentile). Individuals with medical problems that complicated their anxiety, alcohol/substances abuse were excluded. Participants who had received prior formal training of either EMG-Biofeedback, Transcendental Meditation(T.M.) or Relaxation Training (RT)were also excluded. Patients in the T.M.and the RT group had a longer duration of severe anxiety than the EMG-FB group. The T.M. group were predominantly female(F:M=9:1) compared to 4:7 in EMG group and 3:7 in RT group.

In Shannahoff* 1999), participants were diagnosed Obsessive-Compulsive Disorders according to DSM-III-R with a minimum score of 15 on the Y-BOCS for the total 10 items.The minimum age for inclusion was 14 years old. Patients were excluded if they smoked, had a substance abuse disorder, spinal/physical problems (overweight, seizure disorders, pulmonary disorders, hypertension and other cardiovascular problems). Patients with psychiatric disorders which were considered to be the primary diagnosis i.e. schizophrenia, major depressive disorder, bipolar disorder, mental retardation, anorexia / bulimia nervosa, Tourette syndrome, patients with trichotillomania or nail biting as their only compulsion were also excluded. Patients who were unable to maintain regular transportation to the study site were excluded. In the Kundalini Yoga group, patients had more associated physical disease (4:1) and more previous behaviour therapy (5:1) when compared to Relaxation/Mindfulness Meditation. Patients in the Relaxation/Mindfulness Meditation group had more psychiatric history (7:4).

Outcomes
Most outcomes used well established psychiatric rating scale (Symptom Checklist-90, Taylor Manifest Anxiety Scale, Y-BOCS, Profile of Mood Scale etc.). The study by Raskin 1980 also used electromyography from different parts of the body.

All outcome measures were in continuous variables.
The outcome data of Raskin 1980 were described by covariate adjusted means and F-statistics,p-value and graphs. The standard deviation of the endpoint score could not be calculated from the data given. All data were put into the "other data" category.
The outcome data of Shannahoff* 1999 were adequately given for analysis. The study provided both 3 month end-point scores and change scores. In spite of the baseline Y-BOCS seeming to be unequal (but not reaching statistical significant difference p>0.05) , the change score with SD were used in analysis.

METHODOLOGICAL QUALITY

According to the quality criteria, the study by Raskin (1980) was classified as "Moderate quality" as the inclusion and exclusion criteria were clearly defined. Randomisations were assigned to each patient, but the allocation concealment was not explicitly described (unclear) = " B" . The participants gave the commitment not to begin any treatment which would affected their anxiety levels. The important baselines were comparable except the T.M. group had more female patients M:F = 1:9. The dropouts were not described and were not included in the analysis. The outcome measures were clearly defined and valid.

The study of Shannahoff* 1999 was classified as "Moderate quality". The inclusion and exclusion were clearly defined. Using coin toss for each individual patients separately, the allocation of treatment for the next patients could not be predicted, so the allocation concealment was automatically done in this case = "C". One of the important baselines (previous Behavioural Therapy) in 2 groups was very different (Kundalini:Relaxation/Mindfulness Meditation = 5:1) and the data of dropouts were not included in analysis at the 3^{rd} month . The treatment programme, other than the interventions, were controlled to be identical. However, patients would be allowed to reduce or eliminate their established medications, the number of cases who dropped their medications and the effects of medications were not reported . The outcome measures were well accepted and properly done.

Masking/Blinding was not used in quality criteria.

Dropouts
The rate of dropouts in these 2 studies were high.
In Raskin(1980), at the early phase, the dropouts were 18 from 55 (33%) no details given for these 18 dropouts.
Further drop out during the treatment phase were 6 out of 37 (16%) 1 dropped out from EMG-FB, 3 from T.M. and 2 from RT group. The total drop out rate was 44%.
In Shannahoff* 1999 the drop out rate was 7 out of 21 (33%) , 4 from Kundalini and 3 from Relaxation/Meditation group.

RESULTS

Transcendental meditation versus Muscle Biofeedback and versus Relaxation Training in anxiety neurosis

Improvement in symptoms

One study compared the effectiveness of transcendental meditation, muscle biofeedback and relaxation training (Raskin 1980). Due to limitations in the data, with the authors unable to provide any further numeric data (Chan-Ob 2004) it was only possible to reprt the findings narratively. The study showed the effectiveness of three parallel group treatments in an 18 week program. At baseline, the Taylor Manifest Anxiety Scale Score(TMAS) was significantly different between the three groups and a covariate analysis with repeated measures was used to adjust baseline differences. Participants in all three groups had improved on the TMAS scale (F=7.26; df= 1,27; P<0.01), Current Mood Checklist(CMC) by periods (F=24.03; df= 1,27; P<0.01) and by weeks (F=4.43; df= 10, 280; P<0.05). Situational anxiety and symptomatic distress were also improved significantly (P<0.01). Sleep disturbance had not significantly improved. Electromyography which represented the degree of muscle relaxation had also reduced indiscriminately

in the three groups by periods (F=4.4; df = 2,54; P<0.05) and by measures (F=90.25; df = 2,54; P<0.001). In the Social Ratings Scale, there was improvement in work, social functioning and relations with their family of origin (P<0.05), however marital relations and sex life were not significantly changed. The 13 top-rank of patients (N=31) who showed substantial improvement accounted for 40 % of all patients who received treatment. There was no differential effect between the 3 treatments in reducing anxiety in any of measurements. Raskin 1980 also stated that the three treatments were similar with respect to both the time course for obtaining therapeutic results and the subjects' ability to maintain the results which were obtained. The precision of the results could not be determined as 95% confidence intervals were not reported, and could not be calculated due to lack of data.

Acceptability of treatment
There were no reports of adverse events.

Dropout
In the early treatment phase, the dropouts comprised 18 out of 55 participants (33%). No reasons were given for these 18 dropouts. A further 6 of the 37 remaining participants (16%) dropped out during the treatment phase. 1 dropped out from EMG-FB, 3 from TM and 2 from the RT group. The total dropout rate was 44%.

Kundalini Yoga versus Relaxation/Mindfulness meditation in Obsessive-Compulsive Disorders

Improvement in symptoms
One study (Shannahoff* 1999) compared Kundalini Yoga, specifically designed to treat OCD to Relaxation/Mindfulness Meditation, considered to be less active. The baseline of the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) scores of the two groups seemed to be equal, even when re-calculated after excluding those who dropped out. From six scales of measurement change, end-point scales at 3 months were used. The Y-BOCS, considered to be the primary outcome, showed no statistically significant difference between groups (WMD -2.57 95%CI = -7.67 to 2.53). But another 2 scales, the Perceived Stress Scale and Purpose In Life, showed significant differences favouring Kundalini Yoga over Relaxation/MM (WMD -7.57, 95% CI= -13.06 to -2.08; WMD 17.15 , 95%CI= 0.80 to 33.5, respectively). The end-point scores of Symptom Checklist-90-R(SCL-90-R), Global Severity Index and Profile of Mood Scale were markedly skewed so that the data could not be included in a meta-analysis.

Acceptability
There were no reports of adverse events .

Dropout
Seven out of 21 participants (33%), dropped out of the study by (Shannahoff* 1999), 4 from the Kundalini Yoga group and 3 from Relaxation/Meditation group.

DISCUSSION

This review investigated the effectiveness of meditation therapy programs (concentrative meditation and mindfulness meditation), which have been designed specifically to treat anxiety disorders. There are some points regarding meditation and the studies included in this review that need some consideration.

The number of participants who adhered to the protocol is an important first point to consider. In the study by Shannahoff* 1999, 14 out of 21 (67 %) participants completed the treatment program and in the study by Raskin (1980), 31 out of 55 participants (56%) completed the whole course of treatment program. The dropout rate was quite high in both studies, therefore adherence to meditation therapy in the clinical setting may be a major issue. An interesting comment is made by a consumer on the RemedyFind Website: "The problem with meditation, as with exercise, is that depression and anxiety can prevent you from trying them.... if you can't sit still long enough to close your eyes and relax, you can't meditate. If you can't drag yourself out of the house to exercise, you don't do it. If you can, however, both work well when done on a regular basis -- that's the key, though, to their effectiveness" (Morgan 2005). When implementing meditation in the clinical setting, adherence is one significant determinant of effectiveness. The intensiveness and adherence to doing regular meditation are other points of consideration, as with dose-response in medication studies. Delmonte 1998 found that by the end of two years, roughly half (54%) of the patients had terminated meditation. Following the success of psychopharmacological treatment of anxiety disorders, the use of psychosocial treatment prescriptions for anxiety disorder, not only relaxation/meditation but also cognitive-behavioural therapy and dynamic psychotherapy, is reported to have declined between 1991-1996 (Goisman 1999). Unfortunately the reasons for dropout were not provided in the trials included in this review, which preclude further interpretation of the findings.

A second point of consideration in this review is the scarcity of research. We did not find any eligible studies from eastern countries, considered to be the origin of most meditation techniques, especially India, China and Thailand. On the contrary, the only two included studies were done in the United States, following the spread of eastern spirituality to the West in later half of the last century (Snaith 1998). The first well known meditation technique, called Transcendental Meditation (TM) was brought to the United States by Maharishi Mahesh Yogi during the 1960s (Barrows 2002) and it was considered to be the beginning of well systematised meditation practice in the West. The lack of studies from eastern countries might be due to unpublished studies, or studies published in non-indexed journals or studies with negative findings (file drawer effect), which may not yet have been identified.

Thirdly, the eastern religions and meditation techniques have been developed for many thousands of years and were taught both in the old scriptures and through guru (master)-disciple relationships, which are very deeply connected beyond the intellectual understanding of science. The teachings of authoritative masters have not previously needed to be proved. Scientific methods based on hypothetico-deductive reasoning were developed much later. In some organisations, it is discourteous and sometimes inappropriate to question the teaching of the guru. In comparison, the diagnostic system of mental disorders, was developed in the last century. DSM-I, the original manual published by the American Psychiatric Association to set forth diagnostic criteria, was published in 1952. It was replaced in 1968 by DSM-II and followed with DSM-III , DSM-III-R,DSM-IV in(1994) and DSM-IV-TR (2001) respectively (Moon 2004). After the diagnostic systems were formally established, the treatments in modern medicine were concurrently developed and tested, leaving the age-old self help strategies untested or inadequately verified. It may need time and enthusiastic interests to bring this age old traditional wisdom to be tested and accepted in the new frame of western-oriented medicine . As Herbert Benson said " no innovation but a scientific validation of an age old wisdom" (Benson 1976). Although meditation was historically associated with religious or spiritual movements, this is no longer always the case. It is now very necessary to confirm the effectiveness of these meditation techniques if we want to adopt their use for psychiatric patients. Nowadays there are increasing numbers of organisations which use more scientific-based, less mystical terms to identify their techniques.
The best way to prove the effectiveness of meditation techniques should be based on non-cult, faith-free and specifically designed methods to treat patients.

When considering the 2 studies included in the review, the overall number of patients totalled only 45 subjects, and the studies compared different methods of meditation, therefore it was not appropriate to pool the effects together. The study by Raskin 1980 showed a reduction in anxiety scale and EMG score which reflected the effectiveness of treatment of all 3 treatment strategies. No superiority among methods was found. It could be said that any method which helps patients sit calmly in a low arousal environment and induces a relaxation response in various means would equally bring benefit to patients with anxiety disorders. However, participants in this study were highly motivated to practice a self regulatory method which is not always the case for anxiety patients in other settings. Several studies reported that yoga may reduce anxiety and stress and improve mood in healthy people who practice yoga several times per week for 30 to 60 minutes. The mechanism of meditation and another relaxation techniques in decreasing arousal state have been studied. Solberg reported that meditation reduced the level of heart rate and within participant variability of heart rate more than rest but blood pressure was unaffected (Solberg 2004, Canter 2004). If comparing TM to EMG-biofeedback, TM would have some advantages, in that it does not require sophisticated equipment and can be practiced at home. However TM is bound with cult/spiritual organisations and uses a specific Sanskrit mantra, which has to be kept secret. The aims of TM are not only a state of well-being, but also the spiritual development of individuals, which is beyond the scope of this review.

The study by Shannahoff* 1999 showed no statistically significant difference in favour of Kundalini Yoga but the finding was of low precision (the confidence interval was large). After excluding dropout cases, the newly calculated baseline Y-BOCS scores showed a non-significant difference between groups with higher scores for the Kundalini group and the authors had tried to use two-way mixed model analysis of variance to adjust the baseline difference. Post hoc statistical adjustment might not be appropriate because of the small number of subjects (n=7). Due to higher baseline scores, the Kundalini group had the potential to achieve a larger treatment effect than the Relaxation/Mindfulness Meditation group when using the change scores. When calculating the treatment effect by using the end-point score, Kundalini Yoga patients showed no statistically significant improvement in Y-BOCS. However, further larger well designed studies using intention-to-treat analysis are needed before a firm conclusion could be drawn.

Shannahoff-Khalsa has described a specific technique called "The Obsessive-Compulsive Disorder Breath (OCDB)", by blocking the right nostrils and inhaling slowly and deeply through the left nostril; hold in long; exhale slowly and completely through the same nostril. The mental focus should be on the sound of the breath (Shannahoff* 2003). This slow breathing technique is one of many methods of pranayama (Yogic breathing meditation) which are widely practiced and long known in the East. In an anxiety state, the respiration becomes faster and more shallow. As in hyperventilation syndrome, breathing control could inhibit the vicious cycle of hyperventilation. In the case of OCD, there is a question regarding the mechanism of how OCDB can relieve OCD symptoms. A study by Arambula, showed more alpha-EEG (more relaxed state) activity during Kundalini Yoga meditation, compared to the pre-meditation and post-meditation (Arambula 2001). Increasing of alpha rhythm might related to relaxed state. It is suggested that Right Nostril Yogic Breathing (RNB), increases the function of the brain on the right side, implying a possible application of RNB in certain psychiatric disorders with cerebral hemispheric imbalance (Raghuraj 2004). Further explanations need to be explored.

The trials included in this review used 4-18 month follow-ups with a high dropout rate. The adverse events associated with meditation were not reported in either trials. Although meditation has a face value of safety, there are many reports about the adverse events. Castillo reported that meditation can cause depersonalization and derealization (Castillo 1990), and there have been several reports about the association between meditation and psychotic state (French 1975, Lazarus 1976, Walsh 1979, Chan-Ob 1999). The majority of the meditation induced psychosis had underlying

schizophrenia or other psychosis (Chan-Ob 2004). However from the 3 year follow up study by Miller, there were no adverse effects among the practitioners of Mindfulness Meditation using Kabat-Zinn's methods (Miller 1995).

There is a known report of spontaneous pneumothorax caused by pranayama (forced respiration). Adverse side effects can occur when the body is pushed to physiologic extremes (Johnson 2004). In the method of Kundalini Yoga described by Shannahoff-Khalsa, the patient is instructed to make every effort to maximize the four phase of the breath cycle until the complete breath cycle equals 1 minute, with four respective phase each lasting 15 seconds (Shannahoff* 1999; Shannahoff* 2004), the patients had to hold breathing in the state of relative hypercapnia and hypoxia. Miyamura reported that the ventilatory response to hypercapnia and arterial blood gases during Ujjayi respiration(victorious breath) of once per minute for an hour were determined in a professional hatha yogi (Miyamaru 2002). The results suggested that lower chemosensitivity to hypercapnia in yoga practitioners may be due to an adaptation to low arterial pH and high Pa-CO_2 for long periods (Miyamaru 2002; Spicuzza 2001). We do not yet know the risk/benefit of this adaptation in the long term and should be aware that this may be an important issue that could not be addressed in the current review due to lack of data on adverse events provided in the two included studies.

Due to a lack of available studies for inclusion, the current review is unable to directly address whether meditation or medication exerts a larger effect in anxiety disorders. It is acknowledged that caution has to be taken when studying the effect of meditation with the other care without medication, as nowadays medication use in the treatment of anxiety disorders is well established.

AUTHORS' CONCLUSIONS

Implications for practice

1. For patients with anxiety disorders
The small number of included studies and lack of high quality trials in this review do not permit firm conclusions to be drawn. In one moderate quality trial, the use of meditation therapy in anxiety disorder was associated with some reduction of anxiety symptoms in general, which was comparable to another form of relaxation therapy. Motivation and adherence to practice under supervision of a qualified therapist are essential ingredients.There is a lack of evidence to demonstrate the effectiveness of meditation therapy over drug therapy, standard care or another psychotherapy. It is important to delineate between meditation that is a part of religious/spiritual practice and meditation for psychiatric treatment. One randomised controlled trial of small sample size and of moderate study quality suggests that Kundalini Yoga is no more effective than Relaxation/Mindfulness meditation. Kundalini Yoga needs physical effort and is not suitable for patients with cardiovascular disease, respiratory disease or physically unfit people. Patients must be supervised by skilled therapists. Patients should consult their health care provider if they are considering starting yoga or meditation (MC 2003).

2. For clinicians
There is slight supporting evidence for the effectiveness of meditation therapy in anxiety disorder patients, but it is not yet strong enough for any firm conclusions to be drawn. To apply meditation therapy the knowledge, attitude and skill of the therapists should be considered. The value judgement and willingness of individual patients are important factors which should not be overlooked and should always be taken into account. Many methods of meditation have not yet been proven effective for anxiety disorders. Kundalini Yoga for the treatment of OCD shows no benefit for obsessive-compulsive symptoms and more large trials are stll needed. Such techniques need proper training and practice, they may encounter some cultural barriers, and may not be applicable in every setting. The names of specific techniques derived from old scripture language might inevitably be an obstacle, because patients might not want to get involved with some strange-sounding mystical religions. Some techniques have adapted to use more religious-free and scientific-based terms such as Consciousness Transformation, Mindfulness-Based Stress Reduction Program (Kabat-Zinn 1992), Heartmath etc which might be more accepted by patients (Heartmath 2005). If meditation proves to be effective for anxiety disorders, it would have biological plausibility to generalize to anxiety in various clinical contexts.

3. For policy makers
Meditation therapy might hold some promise of providing a useful adjunct to traditional treatment for patients with anxiety disorders, however the scarcity of randomised controlled trials, limited to only two small trials at this time, demand caution to implement it on a large scale basis. There is still a need for data from large randomised controlled trials to verify these initial findings. A cost/benefit analysis would enable clinicians and funders to manage an efficient service and make the best use of resources. The advantage of self-management using meditation includes the reduction in therapists' time, which has not only financial implications but also confers the ability to offer help to large numbers of people (Snaith 1998).

4. For funders of research
More large well designed clinical trials are needed. Comparisons of meditation therapy with other psychotherapy would seem of particular interest. As patients attending for meditation therapy could develop a self regulatory strategy to cope with anxiety in the long term, this may help preserve medical care resources.

Implications for research

It is challenging to do research in meditation therapy. Meditation therapy could be applied to be a form of non-pharmacologic treat-

ment which can promote a sense of mastery and control which usually has been lost in chronic anxiety patients.

Future trials should be registered on a clinical trials registry before recruiting patients into the study. The informed consent process should be adhered to for best understanding and compliance to treatment of the patients. Use of well established diagnostic criteria systems that are properly implemented by trained personnel would help guarantee clinical homogeneity. Diagnosis should be done by physicians familiar with diagnostic systems in psychiatry. Structured or semi-structure diagnostic interviews i.e. Structured Clinical Interview for DSM-III-R (Skre 1991), Composite International Diagnostic Interview (Janca 1994), Schedules for Clinical Assessment in Neuropsychiatry (Wing 1990) or Mini-International Neuropsychiatric Interview (Sheehan 1998) could help enhance the validity and reliability of diagnosis. DSM classification is assumed to be a theoretical approach to psychiatric disorders, whereas phenomenology of symptoms is used to differentiate between different types of anxiety disorders. However, pooling the results from different types of anxiety disorders might cause significant heterogeneity and make it difficult to interpret the results. Using binary outcomes would help the interpretation of clinical improvement and determine the number needed to treat. Merely reporting the statistically significant difference is not enough, and the clinical level of significance should be pre-defined to ensure the true clinical benefits and the strength of association are represented. More objective outcomes should be used i.e. EMG, respiratory rate and variability, heart rate and variability, EEG-alpha feedback etc.

Another important issue in designing meditation trials is to ensure that patients assimilate the techniques properly and adhere to the technique under investigation without the use of another intervention which might pre-exist in the patient's routine life eg prayer, chanting, Yoga Asana (body posture of yogic practice) etc.

It remains crucial to determine the factors which predict the response to meditation, and to delineate whether certain meditations are more effective for particular symptom sets (including symptoms such as generalized anxiety, panic, obsessive-compulsive or phobic). Due to the variety of meditation techniques, it is essential to define the active ingredients of each method. Trials should also study levels of adherence to treatment. The motivating factors of practitioners that could affect effectiveness are also important. The long term benefits of meditation practice for anxiety disorders and mental health in general are also of interest.

Hopefully additional randomised controlled trials of meditation in anxiety disorders will be included in this review in future. Given the high prevalence of anxiety disorders, the suffering of the patients, its chronicity and morbidity, and the enormous personal and societal costs, additional prospective research on meditation therapy is clearly required.

POTENTIAL CONFLICT OF INTEREST

TK runs the Meditation Therapy Clinic for various types of patients at the Department of Psychiatry, Faculty of Medicine, KhonKaen University, Thailand.
No potential conflict of interest for other authors.

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Peter H Canter MD had sent some references of his work.
Vladimir Antonov, Ph.D. (in Biology), Russia at The Religious Book For God Seekers.

List of contacted organizations:
Association for the Advancement of Psychosynthesis Meditation Groups, Inc.
Brahma Kumaris World Spiritual University
Holistic Online.com
Institute of HeartMath
Scandinavian Yoga and Meditation School
Sri Ram Chandra Mission
The Art of Living Foundation
Transcendental Meditation organization and sub-organization
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** Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**Raskin 1980**
Methods	Randomised Controlled Trial

Characteristics of included studies (*Continued*)

	3 parallel group Analysis by analysis of variance with repeated measure, using baseline measures as covariate, factors were groups, time, weeks, period no Intention to treat analysis
Participants	Diagnosis of Anxiety Neurosis (DSM-II) have had symptom for 1 year or more + Taylor Manifest Anxiety Scale (TMAS) score at least 21(80 percentile) Subjects who taking anti-anxiety medication were included Baseline demographic Age (SD) : EMG Feedback(EMG) = 32(6.4) , Transcendental Meditation (TM) = 32(10.2) Relaxation Training(RT) = 37(11.5) Duration of severe anxiety EMG = 10(8.4) TM = 32(10.2) Rt = 37(11.5) Receive medication EMG = 2 TM= 2 RT = 2 Gender M:F EMG = 4:7 TM = 1:9 RT = 3:7 Prior therapy for anxiety EMG = 9 TM = 10 RT = 10 n =55 , 18 drop out early during baseline or immediate after treatment were assigned Further 6 drop outs during treatment periods (3 TM, 2 RT, 1 EMG-BF) Excluded : medical problems that complicated anxiety, alcohol or substance abuse , prior formal training in either EMG-BF, TM, RT
Interventions	Group1 : Muscle Biofeedback (n=11) 3 times/week , 1 hr session used own strategies to relax, modified progressive relaxation , visual imagery , practice twice daily for 20 mins. Group2 : Transcendental Meditation (n=10) 4 consecutive days of individual instruction, lecture , weekly checked by TM trainer, practice twice daily for 20 mins. discourage the use of meditation to relieve anxiety at specific times Group3 : Relaxation Therapy (n=10) similar to Muscle biofeedback but no feedback were provided , practice twice daily for 20 mins The period of treatment consists of 6 weeks baseline , 6-weeks treatment , 6 weeks posttreatment , later follow up at 3,6,12,18 months
Outcomes	1. Anxiety Measures Trait Anxiety - Taylor Manifest Anxiety Scale at prior to treatment, the end of treatment, post treatment observation period State Anxiety - Current Mood Checklist (CMCL) Situational Anxiety- 4 point scale (absent, mild, moderate and severe) Anxiety Symptoms - 4 points scale Sleep disturbance - record daily for sleep latency, time awake, use of sedatives 2. Electromyographic Recordings 3 times a week in all participants Frontalis m., dominant forearm extensor, nondominant forearm flexor - calculated mean peak to peak of EMG waves 3. Social Ratings The Structured and Scaled Interview to Assess Maladjustment
Notes	Participants using anti-anxiety drugs were equally distributed no details given for 18 drop outs at the early phase, the total drop outs are 24 from 55 (44%) Dropouts during the treatment phase 6 in 37 (16%) Data from follow up period were mixed up all treatment so that it could not be differentiate effects of each treatments
Allocation concealment	B – Unclear

Study	**Shannahoff* 1999**
Methods	Randomised Controlled Trial using coin toss by each participants at the beginning 2 phase of treatment : phase 1 RCT 3months + phase 2 uncontrolled trial 12 months blinded participants to treatment group during phase 1

	Analysis : two tailed student's t-test with change score for phase 1 repeated measure ANOVA for phase 2 5. The Intention -to-treat analysis were done by LOCF in each group by paired t-test
Participants	Diagnosis of Obsessive-Compulsive Disorder (DSM-III-R) N = 21 (phase 1) Gender distribution : Kundalini(K) M 3: F 8 Relaxation/ Meditation(R/M) M 4: F 6 Age (SD) K= 38.55 (13.25) R/M= 40 (14.3) Baseline score(Y-BOCS)n=10 K = 22.75(5.15) R/M = 22.80(5.39) Associate physical dz. K = 4 R/M= 1 Psychiatric history K= 4 R/M= 7 Depression K= 3 R/M= 5 Bipolar K=0 R/M=1 ADD K=1 R/M=0 Anorexia-bulimia : K= 1 R/M=1 Previous Behavioural Therapy K =5 R/M = 1 Relative with OCD K = 3 R/M =3 Medication K= 8 R/M = 9
Interventions	Group 1 : Kundalini Yoga practice weekly meeting with instructors, Protocol required approximate 1 hour to complete and daily practice to the best of their ability(n=11) Group 2 : Relaxation Response 30 mins + Mindfulness Meditation 30 mins , and daily practice to the best of their ability.(n=10)
Outcomes	Yale-Brown Obsessive Compulsive Scale : obsession , compulsion , total score : self rating after explanation in group SCL-90 R include obsessive-compulsive scale , GSI composite(total) Profile of Mood Scale (POMS) represented by Total Mood Disorder index(TMD) Perceived Stress Scale (PSS) Purpose In Life (PIL)
Notes	This review include only phase 1 which was RCT. After phase 1 all patients were merged into one group Kundalini Attrition rate 7 in 21 (33%) , 4 from Kundalini and 3 from Relaxation/Meditation group The baseline score of Y-BOCS were re-calculated for the remaining participants(n= 7 in each group) K= 24.57(4.68) , R/M = 20.57(3.36) The end point score(Mean(SD)) at 3 months obtained from remaining 7 participants in each group
Allocation concealment	C – Inadequate

Characteristics of excluded studies

Study	Reason for exclusion
Lu 1998	Pseudo-randomization , alternate patients
Sahasi 1989	Pseudorandomization , odd-even number and subject to willingness , some participants in group yoga if unable to practice moved to drug group

ANALYSES

Comparison 01. Kundalini Yoga versus Relaxation Response/Mindfuness Meditation

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Symptom improvement (Y-BOCS) at 3 months	1	14	Weighted Mean Difference (Fixed) 95% CI	-2.57 [-7.67, 2.53]
02 Perceived Stress Scale at 3 months	1	14	Weighted Mean Difference (Fixed) 95% CI	-7.57 [-13.06, -2.08]
03 Purpose in Life at 3 months	1	14	Weighted Mean Difference (Fixed) 95% CI	17.15 [0.80, 33.50]
04 Symptoms Checklist-90-Revised			Other data	No numeric data
05 Global Severity Index Scale			Other data	No numeric data
06 Profile Mood States			Other data	No numeric data

Comparison 02. EMG-feedback versus Transcendental Meditation versus Relaxation training

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Taylor Manifest Anxiety Scale			Other data	No numeric data
02 Current Mood Checklist			Other data	No numeric data
03 Situations, Symptoms and Sleep			Other data	No numeric data
04 Electromyography			Other data	No numeric data
05 Social Ratings			Other data	No numeric data

INDEX TERMS

Medical Subject Headings (MeSH)

Anxiety Disorders [*therapy]; Biofeedback (Psychology); Meditation [*methods]; Obsessive-Compulsive Disorder [therapy]; Randomized Controlled Trials; Relaxation Techniques; Yoga

MeSH check words

Humans

COVER SHEET

Title	Meditation therapy for anxiety disorders
Authors	Krisanaprakornkit T, Krisanaprakornkit W, Piyavhatkul N, Laopaiboon M
Contribution of author(s)	TK 04 : develop protocol, searching, quality assessment, data collection, analysis, WK04 : searching, quality assessment, data collection NP04 : searching , quality assessment ML04 : analysis
Issue protocol first published	2004/4
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What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
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GRAPHS AND OTHER TABLES

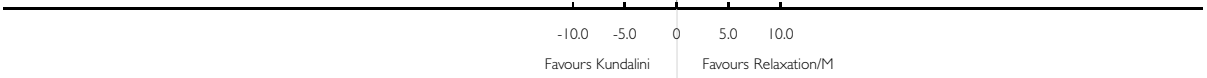
Analysis 01.01. Comparison 01 Kundalini Yoga versus Relaxation Response/Mindfuness Meditation, Outcome 01 Symptom improvement (Y-BOCS) at 3 months

Review: Meditation therapy for anxiety disorders

Comparison: 01 Kundalini Yoga versus Relaxation Response/Mindfuness Meditation

Outcome: 01 Symptom improvement (Y-BOCS) at 3 months

Study	Kundalini Yoga N	Kundalini Yoga Mean(SD)	Relax/MindfulMed N	Relax/MindfulMed Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Shannahoff* 1999	7	15.14 (6.20)	7	17.71 (2.98)		100.0	-2.57 [-7.67, 2.53]
Total (95% CI)	7		7			100.0	-2.57 [-7.67, 2.53]
Test for heterogeneity: not applicable							
Test for overall effect z=0.99 p=0.3							



Analysis 01.02. Comparison 01 Kundalini Yoga versus Relaxation Response/Mindfuness Meditation, Outcome 02 Perceived Stress Scale at 3 months

Review: Meditation therapy for anxiety disorders

Comparison: 01 Kundalini Yoga versus Relaxation Response/Mindfuness Meditation

Outcome: 02 Perceived Stress Scale at 3 months

Study	Kundalini Yoga N	Kundalini Yoga Mean(SD)	Relaxation/Mindfulne N	Relaxation/Mindfulne Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Shannahoff* 1999	7	14.29 (5.76)	7	21.86 (4.67)		100.0	-7.57 [-13.06, -2.08]
Total (95% CI)	7		7			100.0	-7.57 [-13.06, -2.08]
Test for heterogeneity: not applicable							
Test for overall effect z=2.70 p=0.007							

Analysis 01.03. Comparison 01 Kundalini Yoga versus Relaxation Response/Mindfuness Meditation, Outcome 03 Purpose in Life at 3 months

Review: Meditation therapy for anxiety disorders

Comparison: 01 Kundalini Yoga versus Relaxation Response/Mindfuness Meditation

Outcome: 03 Purpose in Life at 3 months

Study	Kundalini Yoga N	Kundalini Yoga Mean(SD)	Relaxation/Mindfulne N	Relaxation/Mindfulne Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Shannahoff* 1999	7	107.29 (18.65)	7	90.14 (11.81)		100.0	17.15 [0.80, 33.50]
Total (95% CI)	7		7			100.0	17.15 [0.80, 33.50]
Test for heterogeneity: not applicable							
Test for overall effect z=2.06 p=0.04							

Analysis 01.04. Comparison 01 Kundalini Yoga versus Relaxation Response/Mindfuness Meditation, Outcome 04 Symptoms Checklist-90-Revised

Symptoms Checklist-90-Revised

Study	Results	Statistics	Notes
Shannahoff* 1999	changed score shown statistical significant different favoured Kundalini Yoga	Endpoint score gr1: 0.957 (0.635)(1.54 to 0.37) gr2 : 1.929 (0.512)(2.40 to 1.46) n = 14 (7/7)	Skewed data

Analysis 01.05. Comparison 01 Kundalini Yoga versus Relaxation Response/Mindfuness Meditation, Outcome 05 Global Severity Index Scale

Global Severity Index Scale

Study	Results	Statistics	Notes
Shannahoff* 1999	Changed score shown Statistical significant different (p<0.05) favoured Kundalini Yoga	Endpoint score gr1: 0.497 (0.328)(0.800 to 1.93) gr2: 1.106 (0.390)(1.46 to 0.74) n =14 (7/7)	Skewed data

Analysis 01.06. Comparison 01 Kundalini Yoga versus Relaxation Response/Mindfuness Meditation, Outcome 06 Profile Mood States

Profile Mood States

Study	Results	Statistics	Notes
Shannahoff* 1999	Changed score shown statistical significant different (p<0.05) favoured Kundalini Yoga	Endpoint score gr1: 16.43 (29.71)(43.90 to -11.05) gr2: 70.14 (31.47)(99.25 to 41.04)	Skewed data

Analysis 02.01. Comparison 02 EMG-feedback versus Transcendental Meditation versus Relaxation training, Outcome 01 Taylor Manifest Anxiety Scale

Taylor Manifest Anxiety Scale

Study	Results	Statistics	Notes
Raskin 1980	- There was no significant group effect, - The test time were significant different	(F =7.26; df= 1,27; P<0.1)	- Covariance adjusted means decrease significantly by time - no different between different type of treatment

Raskin 1980

Analysis 02.02. Comparison 02 EMG-feedback versus Transcendental Meditation versus Relaxation training, Outcome 02 Current Mood Checklist

Current Mood Checklist

Study	Results	Statistics	Notes
Raskin 1980	- no significant group effect , period of treatment were significant different , - weeks by periods also significant different	- periods F= 24.03; df = 2,56 ; P<0.01 - weeks by period F =4.43; df = 10,280; P<0.05	

Raskin 1980

Analysis 02.03. Comparison 02 EMG-feedback versus Transcendental Meditation versus Relaxation training, Outcome 03 Situations, Symptoms and Sleep

Situations, Symptoms and Sleep

Study	Results	Statistics	Notes
Raskin 1980	- No significant group effect - Situational anxiety and symptomatic distress	- Situational and Symptomatic distress : P<0.01 from baseline to post-treatment period	

Situations, Symptoms and Sleep (*Continued*)

Study	Results	Statistics	Notes
	decreased significantly - Sleep disturbance was no significant improvement		
Raskin 1980			

Analysis 02.04. Comparison 02 EMG-feedback versus Transcendental Meditation versus Relaxation training, Outcome 04 Electromyography

Electromyography

Study	Results	Statistics	Notes
Raskin 1980	- EMG scores from each musclewere averaged to give one score ; - The factors were groups, periods, and measures - There were no significant group effect or interaction . - Periods were significant different. Measures were significant different -The posttreatment period frontalis scores remained significant lower than baseline period	- Periods (F= 4.4; df= 2,54; P<0.05) - Measures (F= 90.25; df= 2,54; P< 0.001) and rose significantly from treatment period to post-treatment period (P<0.01) - The posttreatment period frontalis scores P<0.01	

Analysis 02.05. Comparison 02 EMG-feedback versus Transcendental Meditation versus Relaxation training, Outcome 05 Social Ratings

Social Ratings

Study	Results	Statistics	Notes
Raskin 1980	- In all ratings,the groups were not statistical different. - Work, social functioning, relations with family significant improve from pre-treatment - marital relations and sex life , no significant change were found	P< 0.05	

Pneumococcal vaccination during pregnancy for preventing infant infection (Review)

Chaithongwongwatthana S, Yamasmit W, Limpongsanurak S, Lumbiganon P, DeSimone JA, Baxter J, Tolosa JE

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Pneumococcal vaccination during pregnancy for preventing infant infection (Review)

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ABSTRACT

Background
Each year at least one million children worldwide die of pneumococcal infections. The development of bacterial resistance to antimicrobials adds to the difficulty of treatment of diseases and emphasizes the need for a preventive approach. Newborn vaccination schedules could substantially reduce the impact of pneumococcal disease in immunized children, but does not have an effect on the morbidity and mortality of infants less than three months of age. Pneumococcal vaccination during pregnancy may be a way of preventing pneumococcal disease during the first months of life before the pneumococcal vaccine administered to the infant starts to produce protection.

Objectives
To assess the effect of pneumococcal vaccination during pregnancy for preventing infant infection.

Search strategy
We searched the Cochrane Pregnancy and Childbirth Group Trials Register (June 2004), CENTRAL (*The Cochrane Library*, Issue 2, 2004), MEDLINE (January 1966 to June 2004), EMBASE (January 1985 to June 2004), and reference lists of articles.

Selection criteria
Randomized controlled trials in pregnant women comparing pneumococcal vaccine with placebo or doing nothing or with another vaccine to prevent infant infections.

Data collection and analysis
Two authors independently assessed methodological quality and extracted data using a data collection form. Study authors were contacted for additional information.

Main results
Three trials (280 participants) were included. There was no evidence that pneumococcal vaccination during pregnancy reduces the risk of neonatal infection (one trial, 149 pregnancies, relative risk (RR) 0.51; 95% confidence interval (CI) 0.18 to 1.41). Although the data suggest an effect in reducing pneumococcal colonisation in infants by 16 months of age (one trial, 56 pregnancies, RR 0.33; 95% CI 0.11 to 0.98), there was no evidence of this effect in infants at two months of age (RR 0.28; 95% CI 0.02 to 5.11) or by seven months of age (RR 0.32; 95% CI 0.08 to 1.29).

Authors' conclusions
There is insufficient evidence to support whether pneumococcal vaccination during pregnancy could reduce infant infections.

PLAIN LANGUAGE SUMMARY

Not enough evidence to support the use of pneumococcal vaccination during pregnancy for preventing infant infections

Although the incidence of invasive pneumococcal disease is variable across the world, mortality rate is high in children who get this infection. Newborn vaccination schedules could reduce the impact of pneumococcal disease in immunized children, but have no effect on the morbidity and mortality of infants less than three months of age. Maternal pneumococcal immunization during pregnancy may be a method of preventing pneumococcal disease during the infant's first months of life. The review of trials found there was not enough information to say whether pneumococcal vaccination during pregnancy led to fewer infant infections.

BACKGROUND

Infections caused by *Streptococcus pneumoniae* (pneumococcus) are a major cause of morbidity and mortality throughout the world (WHO 1999). Pneumococcus is a leading cause of illness in young children and causes illness and death among the elderly and persons who have certain underlying medical conditions. The organism colonizes the upper respiratory tract and can cause the following types of illnesses: (a) disseminated invasive infections, including bacteremia and meningitis; (b) pneumonia and other lower respiratory tract infections; and (c) upper respiratory tract infections, including otitis media and sinusitis. Invasive pneumococcal infections are less common than non-invasive manifestations, but cause high mortality. Children with invasive disease have a mortality rate as high as 15% to 20% (CDC 1997) and at least one million children worldwide, mostly in low- to middle-income countries, die of pneumococcal infections each year (WHO 1999). The development of resistance to antimicrobials by the bacteria adds to the difficulty of treatment of diseases and emphasizes the need for a preventive approach.

Limited data are available about the worldwide incidence of pneumococcal infections in children. In Finland, the annual incidence of pneumococcal bacteraemic infections was 24.3 per 100,000 among children up to four years of age (Escola 1992). A community-based study carried out in a rural area of the Gambia, West Africa, estimated the incidence of invasive pneumococcal disease to be 554 per 100,000 per year in children under the age of one year, and 458 per 100,000 per year in those less than two years old (O'Dempsey 1996). In the United States, the routine use of pneumococcal vaccine has a substantial impact on the epidemiology of pneumococcal disease in children. In infants younger than one year, rates of invasive pneumococcal disease have decreased from 51.5 to 98.2 cases per 100,000 person-years to 9.4 cases per 100,000 person-years, and in children younger than two years from 81.7 to 113.8 cases per 100,000 person-years to 38 cases per 100,000 person-years (Black 2001).

There are two types of pneumococcal vaccine available, polysaccharide vaccines and polysaccharide/protein conjugate vaccines. The 23-valent polysaccharide vaccine (PPV23) contains polysaccharide antigen from 23 types of pneumococcal bacteria, which cause 88% of bacteraemic pneumococcal disease. More than 80% of healthy adults who receive PPV23 develop antibodies against the serotypes contained in the vaccine within two to three weeks after vaccination; however, the vaccine is relatively poor at producing immunity in children less than two years old (Pomat 1994). The 7-valent pneumococcal conjugated vaccine (PCV7) is much better at producing immunity in infants than pure polysaccharide vaccines (Black 2000; Steinhoff 1994) and is recommended in the United States for immunization of infants (AAP 2000). Newborn vaccination schedules consist of three doses routinely given at two, four and six months of age. A booster dose is recommended at 12 to 15 months of age. After four doses, more than 90% of healthy infants develop antibodies to all seven serotypes contained in the vaccine. In a large trial, PCV7 was shown to reduce invasive disease caused by vaccine serotypes by 97%; however, it was less effective against acute otitis media (Black 2000). Local reactions following PCV7 occur in 10% to 20% of recipients and are more common with the fourth dose than the first three doses. No severe adverse events attributable to PCV7 have been reported. The vaccine could substantially reduce the impact of pneumococcal disease in immunized children (Black 2001; CDC 2000); however, it does not have an effect on the morbidity and mortality of the younger infants, especially those less than three months of age. This may be due to the fact that serum IgG antibodies against polysaccharides increase only after the second and third vaccine doses are administered (Rennels 1998). Additional pneumococcal polysaccharide conjugate vaccines containing 9 and 11 serotypes of *S. pneumoniae* are being developed. In clinical trials (Cutts 2005; Klugman 2003), the 9-valent pneumococcal conjugated vaccine (PCV9) has shown to reduce the incidence of pneumonia and invasive pneumococcal disease among children and was administered to the newborn beginning as early as at six weeks of age.

Maternal immunisation could help to prevent the two to three million neonatal and early infant deaths that occur in low- to middle-income countries each year (Greenwood 2003). Maternal pneumococcal immunization may be a way of preventing pneumococcal disease during the first months of life before infant-administered pneumococcal conjugate vaccine starts to produce protection. This strategy has the potential to impact on public health, as has been seen by the prevention of tetanus neonatorum through maternal immunization (Glezen 1998). An effective delivery sys-

tem for maternal immunisation already exists and, because of the success of maternal tetanus immunization, this approach to the prevention of serious illness or death in young infants is widely accepted by the general population. However, the ideal maternal pneumococcal immunization regarding vaccine type (polysaccharide or conjugate), regimen and timing is not known.

OBJECTIVES

To assess the effectiveness of pneumococcal vaccine administered to pregnant women in preventing pneumococcal infection in the infant.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomized controlled trials. Quasi-randomized controlled trials were not included.

Types of participants

Healthy women with uncomplicated pregnancies.

Types of intervention

Pneumococcal vaccine (polysaccharide or conjugate) compared with placebo or doing nothing or with another vaccine.

Types of outcome measures

(1) Incidence of neonatal pneumococcal infection:
(a) Pneumonia (diagnosed by clinical findings and radiological or laboratory findings)
(b) Meningitis (diagnosed by clinical findings and laboratory findings)
(c) Bacteraemia/sepsis (diagnosed by clinical findings and laboratory findings)
(d) Neonatal death (due to pneumococcal infection)
(e) Otitis media (diagnosed by clinical findings and laboratory findings)
(2) Incidence of neonatal pneumococcal colonisation
(3) Neonatal antibody levels
(4) Adverse neonatal effects
(5) Maternal antibody levels
(6) Incidence of maternal pneumococcal colonisation during labour
(7) Adverse maternal effects

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

We searched the Cochrane Pregnancy and Childbirth Group Trials Register (June 2004).

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) monthly searches of MEDLINE;
(3) handsearches of 30 journals and the proceedings of major conferences;
(4) weekly current awareness of a further 37 journals.

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 'Search strategies for identification of studies' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are given a code (or codes) depending on the topic. The codes are linked to review topics. The Trials Search Co-ordinator searches the register for each review using these codes rather than keywords.

In addition, we searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library,* Issue 2, 2004) using the following search strategy.
#1 PREGNANCY*:ME
#2 PREGNAN*
#3 MATERN*
#4 ANTEPART*
#5 PRENATAL
#6 ANTENATAL
#7 PERINATAL
#8 ((((((#1 or #2) or #3) or #4) or #5) or #6) or #7)
#9 PNEUMOCOCC*
#10 PNEUMOCOCCAL*:ME
#11 (#9 or #10)
#12 VACCIN*
#13 VACCINE*:ME
#14 IMMUNUNIZATION*:ME
#15 ((#12 or #13) or #14)
#16 (#11 and #15)
#17 (#8 and #16)

We adapted the above search strategy to search MEDLINE (January 1966 to June 2004) and EMBASE (January 1985 to June 2004) by selecting appropriate MeSH and/or keywords from their respective thesauri.

We did not apply language restrictions and searched cited references from retrieved articles for additional studies. We reviewed abstracts and letters to the editor to identify randomized controlled trials that have not been published. If we identified

a randomized controlled trial, we contacted the primary investigator directly to obtain further data. We reviewed editorials, indicating expert opinion, to identify and ensure that no key studies were missed for inclusion in this review.

METHODS OF THE REVIEW

Two authors screened the studies that were found as a result of the search strategy described earlier. We selected all potential trials for eligibility according to the criteria specified in the protocol. We evaluated trials under consideration for methodological quality using the standard criteria described in the Cochrane Reviewers' Handbook (Alderson 2004). Two authors independently assessed whether the studies met the criteria with disagreements resolved by discussion.

Assessment of trial quality
To avoid potential biases, we assessed trial quality by considering the methods used in each trial:
(1) selection bias - to consider the quality of the random allocation concealment;
(2) performance bias - to consider the quality of the blinding of the intervention;
(3) attrition bias - to consider the quality of completeness of follow up;
(4) detection bias - to consider the quality of the blinding of the outcome assessment.
We based the quality assessment on a systematic assessment of the potential for each of these biases to have occurred.

We assigned a quality rating for the blinding of randomization to each trial, using the criteria outlined in the Cochrane Reviewers' Handbook (Alderson 2004):
(A) adequate; (B) unclear; (C) inadequate; or (D) not used.

We assigned a quality rating of (A) yes; (B) cannot tell; or (C) no, to the other quality components (blinding of intervention, completeness of follow up and blinding of outcome assessment).

Data management and analysis
Two authors independently extracted and double entered the data. We resolved discrepancies by discussion. There was no blinding of authorship. Whenever possible, we asked for clarification of quality issues that were unclear and ask for unpublished data from investigators.

We used the Cochrane Review Manager software (RevMan 2003) for the analysis. For individual trials, where possible, we reported mean differences (and 95% confidence intervals) for continuous variables. For categorical outcomes, we reported relative risk and risk difference (and 95% confidence intervals). For the meta-analysis, we reported relative risk (and 95% confidence intervals) for categorical outcomes.

We conducted the meta-analysis using the fixed-effect model. We assessed heterogeneity using the I^2 statistics for heterogeneity. We interpreted a value of more than 50% as evidence of substantial heterogeneity. Where heterogeneity was found, we looked for an explanation. If studies with heterogeneous results were thought to be comparable, we undertook the statistical synthesis of the results using a random-effects model.

DESCRIPTION OF STUDIES

We identified six studies as potentially eligible for inclusion in this review. Three trials were excluded.

Excluded studies
*See 'C*haracteristics of excluded studies' table.

Included studies
A total of 280 pregnant women participated in the three included studies comparing 23-valent pneumococcal polysaccharide vaccine with control vaccine (Munoz 2001; O' Dempsey 1996; Shahid 1995). Munoz's trial used a 2:1 randomization scheme and had 20 women in vaccine group and 40 women in control group. O'Dempsey's trial had 75 women in each group. Shahid's trial had 36 women in vaccine group and 34 women in control group.

Participants
Included trials conducted in different settings; one in the United States (Munoz 2001), one in Gambia (O' Dempsey 1996) and the other in Bangladesh (Shahid 1995). All participants were healthy women with an uncomplicated pregnancy. Mean age of participants in each study was 30.2, 22.0 and 25.6 years respectively.

Interventions
All trials used 23-valent pneumococcal polysaccharide vaccine compared with control vaccine. Two trials (O' Dempsey 1996; Shahid 1995) used meningococcal vaccine as the control while the other (Munoz 2001) used *Hemophilus influenzae* conjugate vaccine. All women got a single injection of pneumococcal or control vaccine. The mean gestational age at the time of immunization in each study was 38.0, 32.3 weeks and 33.3 weeks, respectively. The mean interval between immunization and delivery in each study was 44.1, 51.4 and 43.6 days respectively.

Outcomes
One study reported the incidence of neonatal infection (O' Dempsey 1996) and the other one reported the incidence of neonatal pneumococcal colonisation (Munoz 2001). All trials reported maternal antibody levels as geometric mean and 95% confidence interval. No serious adverse reactions attributable to the vaccines were observed in all studies (*see* 'Characteristics of included studies').

METHODOLOGICAL QUALITY

The included trials were considered to be of reasonable quality. All trials did not describe the precise method of random allocation; however, all were double-blind studies. No trials had complete follow up.

RESULTS

This review includes data from three trials with a total of 280 pregnant women. A total of 131 women were randomized to be immunized with pneumococcal polysaccharide vaccine and 149 women were randomized to control vaccines.

Neonatal infections
Only one trial (O' Dempsey 1996) with 149 pregnancies reported these outcomes. There was insufficient evidence to show an effect of maternal pneumococcal vaccine in reduction of neonatal infections (relative risk (RR) 0.51; 95% confidence interval (CI) 0.18 to 1.41) including pneumonia (RR 0.58; 95% CI 0.18 to 1.90), meningitis (RR 3.04; 95% CI 0.13 to 73.44), and otitis media (RR 0.14; 95% CI 0.01 to 2.75).

Neonatal pneumococcal colonisation
One study (Munoz 2001) with 56 pregnancies reported this outcome. There was not enough evidence to show an effect of maternal pneumococcal vaccination in reduction of neonatal nasal carriage of pneumococci at two months of age (RR 0.28; 95% CI 0.02 to 5.11) or by seven months of age (RR 0.32; 95% CI 0.08 to 1.29). Nevertheless, the results showed a statistically significant decrease in the incidence of pneumococcal colonisation in infants by 16 months of age (RR 0.33; 95% CI 0.11 to 0.98).

Neonatal and maternal antibody levels
Antibody levels were reported as geometric mean and 95% CI. There were inconsistent results between two studies. One study (Munoz 2001) showed significantly higher immunoglobulin G levels in cord blood and maternal serum in women immunized with pneumococcal vaccine when compared with control vaccine regardless of any serotypes. In contrast, the other study (O' Dempsey 1996) showed significantly higher maternal antibody levels only for serotype 14, but no evidence of an effect of the pneumococcal vaccine resulting in an increase in neonatal antibody levels or maternal antibody levels in the other serotypes.

Adverse maternal effects
The adverse maternal effect that has been reported is tenderness at the injection site (Munoz 2001; Shahid 1995). The RR is 3.20 with 95% CI of 0.32 to 31.54.

DISCUSSION

There are some limitations that should be considered when interpreting the results. First, the allocation concealment was not clearly defined in all included trials. Second, neonatal infection, the most significant outcome, was reported in only one trial. There was no evidence of an effect of pneumococcal vaccination during pregnancy in preventing neonatal infections; however, as previously described, there was only one trial (O' Dempsey 1996) reporting this outcome. The power to detect this effect might be too low because of a small sample size. Results of one study (Munoz 2001) suggested that maternal pneumococcal vaccination can reduce the risk of pneumococcal colonisation by 16 months of age, but no effect was shown at earlier ages. At two months of age, there was no nasal carriage of pneumococci in infants whose mothers were immunized with the pneumococcal vaccine during pregnancy, but the trial also did not have necessary power to detect this effect. The effect at 16 months of age with no effect demonstrated at two or seven months may not be due to the vaccine administered during pregnancy; however, there was no detail regarding the confounding factors or co-intervention reported in the trial. There was also no information on breast feeding or antibody level in breast milk that may impact on antibody transfer to the neonates.

An inconsistent result between two trials (Munoz 2001; Shahid 1995) was shown regarding tenderness at the injection site. This may due to the different control vaccines used in the studies. Although there tends to be increased tenderness among women injected with pneumococcal vaccine, this symptom lasted only a few days after injection and no serious adverse events were reported in all of the trials. Risk to a developing fetus from vaccination of the mother during pregnancy is primarily theoretical. No evidence exists of risk from vaccinating pregnant women with inactivated virus or bacterial vaccines or toxoids (CDC 2002). Benefits of vaccinating pregnant women usually outweigh potential risks when the likelihood of disease exposure is high, when infection would pose a risk to the mother or fetus, and when the vaccine is unlikely to cause harm. Pneumococcal vaccine is recommended to administer to pregnant women when they have the underlying medical conditions for preventing maternal infections (ACOG 2003). None reported risk from the vaccine to fetus.

Recent data indicate that pneumococcal conjugate vaccine given to the children is having a substantial effect in pneumococcal disease in the United States since its introduction in 2000. A large, population-based surveillance system monitoring invasive pneumococcal disease in a population of nearly 20 million persons in the United States, found that rates of invasive pneumococcal disease in children younger than two years of age were 68.6% lower in 2001 compared with rates of disease before the vaccine was introduced (Whitney 2003). Furthermore, widespread vaccination of children with PCV7 has shown a 'herd effect' in decreasing the carriage rate of *S. pneumoniae* in children, who are an important vector of S. pneumoniae to other children and adults (Dagan 2000). Data from the same surveillance indicate that unvaccinated adults are benefiting from vaccination of children. Infection rates in adults fell 8% to 32% when compared with the average rates in 1998 and 1999 (Whitney 2003). Vaccine formulations contain-

ing additional serotypes have been evaluated. A trial of a PCV9 in children starting the first dose at six-weeks of age showed the efficacy of 83% (95% confidence interval (CI) 39 to 97) in reduction of first episode of invasive pneumococcal disease caused by serotypes included in the vaccine (Klugman 2003). A recent trial found the efficacy of 77% (95% CI 51 to 90) against invasive pneumococcal disease caused by vaccine serotypes (Cutts 2005). The vaccine formulations containing additional serotypes (PCV9, PCV11) and earlier administration to the newborn (that is, at birth) may be a considerable option to minimize the invasive pneumococcal disease in children.

This pneumococcal conjugate vaccine is not a routine vaccination to children in any low- to middle-income country. Introduction of pneumococcal conjugate vaccines could potentially represent a major improvement in child health and survival. However, these countries face complex and diverse health priorities with limited financial and human resources. There is a need to develop the financing mechanisms that can provide the affordable vaccines to the low- to middle-income countries.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence from randomized controlled trials to support the use of pneumococcal vaccination during pregnancy for preventing infant infections.

Implications for research

As previously discussed, the future vaccine formulations containing additional serotypes and earlier administration to the newborn are needed to be evaluated the effectiveness on reduction of the invasive pneumococcal disease in children. If it is the case, trial of pneumococcal vaccination during pregnancy for preventing infant infection may not be needed.

POTENTIAL CONFLICT OF INTEREST

None known.

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TABLES

Characteristics of included studies

Study	**Munoz 2001**
Methods	Blinding of intervention: yes. Blinding of outcome assessment: yes. Completeness of follow up: no.
Participants	Country: United States. Number: 20 women in the intervention group and 40 women in the control group.
Interventions	23-valent pneumococcal polysaccharide vaccine vs Hemophilus influenzae type b conjugate vaccine.
Outcomes	Incidence of neonatal and infant pneumococcal colonisation. Neonatal antibody levels (GM). Maternal antibody levels (GM). Incidence of tenderness at the injection site.
Notes	
Allocation concealment	B – Unclear

Study	**O' Dempsey 1996**
Methods	Blinding of intervention: yes. Blinding of outcome assessment: yes. Completeness of follow up: no.
Participants	Country: The Gambia. Number: 75 women in the intervention group and 75 women in the control group.
Interventions	23-valent pneumococcal polysaccharide vaccine vs meningococcal vaccine.
Outcomes	Incidence of neonatal pneumonia. Incidence of neonatal meningitis. Incidence of neonatal otitis media. Neonatal antibody levels (GM). Maternal antibody levels (GM).
Notes	
Allocation concealment	B – Unclear

Study	**Shahid 1995**
Methods	Blinding of intervention: yes. Blinding of outcome assessment: yes. Completeness of follow up: no.
Participants	Country: Bangladesh. Number: 36 women in the intervention group and 34 women in the control group.
Interventions	23-valent pneumococcal polysaccharide vaccine vs meningococcal vaccine.
Outcomes	Maternal antibody levels (GM). Incidence of tenderness at the injection site.
Notes	
Allocation concealment	B – Unclear

GM: geometric mean

vs: versus

Characteristics of excluded studies

Study	Reason for exclusion
Daly 2003	Outcome in the report was enrolment rate.
Glezen 2000	It was an abstract only and there was not enough information in the abstract.
Quiambao 2003	No outcome comparison between study and control group was shown.

ANALYSES

Comparison 01. Pneumococcal vaccine versus control vaccine

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Neonatal infection			Relative Risk (Fixed) 95% CI	Subtotals only
02 Pneumococcal colonisation			Relative Risk (Fixed) 95% CI	Subtotals only
03 Neonatal antibody levels at birth			Other data	No numeric data
04 Maternal antibody levels postvaccination			Other data	No numeric data
05 Adverse maternal effects			Relative Risk (Random) 95% CI	Subtotals only

INDEX TERMS

Medical Subject Headings (MeSH)

Infant, Newborn; Pneumococcal Infections [immunology; * prevention & control]; Pneumococcal Vaccines [* administration & dosage]; Randomized Controlled Trials

MeSH check words

Female; Humans; Pregnancy

COVER SHEET

Title	Pneumococcal vaccination during pregnancy for preventing infant infection
Authors	Chaithongwongwatthana S, Yamasmit W, Limpongsanurak S, Lumbiganon P, DeSimone JA, Baxter J, Tolosa JE
Contribution of author(s)	Surasith Chaithongwongwatthana (SC) designed the review and wrote the protocol. Waralak Yamasmit (WY), Sompop Limpongsanurak (SL), Pisake Lumbiganon (PL), Joseph DeSimone (JD), Jason Baxter (JB), and Jorge Tolosa (JT) provided general advice and approved the published version. SC and WY conducted and drafted the review. SL, PL, JD, JB and JT gave intellectual comments on the review and approved the final version.
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What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	30 June 2004
Date authors' conclusions section amended	Information not supplied by author
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GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Pneumococcal vaccine versus control vaccine, Outcome 01 Neonatal infection

Review: Pneumococcal vaccination during pregnancy for preventing infant infection

Comparison: 01 Pneumococcal vaccine versus control vaccine

Outcome: 01 Neonatal infection

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Pneumonia					
O' Dempsey 1996	4/74	7/75		100.0	0.58 [0.18, 1.90]
Subtotal (95% CI)	74	75		100.0	0.58 [0.18, 1.90]
Total events: 4 (Treatment), 7 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.90 p=0.4					
02 Meningitis					
O' Dempsey 1996	1/74	0/75		100.0	3.04 [0.13, 73.44]
Subtotal (95% CI)	74	75		100.0	3.04 [0.13, 73.44]
Total events: 1 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.68 p=0.5					
03 Otitis media					
O' Dempsey 1996	0/74	3/75		100.0	0.14 [0.01, 2.75]
Subtotal (95% CI)	74	75		100.0	0.14 [0.01, 2.75]
Total events: 0 (Treatment), 3 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.29 p=0.2					
04 All infections					
O' Dempsey 1996	5/74	10/75		100.0	0.51 [0.18, 1.41]
Subtotal (95% CI)	74	75		100.0	0.51 [0.18, 1.41]
Total events: 5 (Treatment), 10 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.30 p=0.2