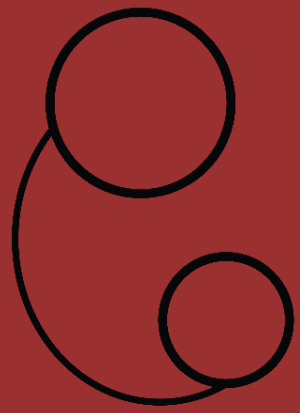
ECRU in the Eastern Cape

18 years of scientific excellence



Effective
Care
Research
Unit

“When you work in an area that has vast shortages, you are able to have a bigger impact. It is extremely satisfying to work in an area where you feel you’re making a difference.”

Justus Hofmeyr

Foreword

"Justus Hofmeyr, founder of the Effective Care Research Unit, is probably one of the most productive South African researchers of our time. His work in research, research synthesis and innovative thinking is unparalleled in the field of maternal and perinatal health globally. He has always been ahead of others in thinking of and evaluating solutions of direct relevance to the health of women and children. His approach to providing respectful maternity care; improving quality of care through the Better Births Initiative and, later on, with the establishment of the onsite midwife-led birth units; titrating misoprostol for safe use during labour; and developing the systematic reviews training course has always been practical and directly relevant to care and capacity strengthening of care providers. Justus has always supported the research and normative work of the World Health Organization by providing insights and advice that is evidence-based, applicable and feasible. His commitment to making a difference is truly inspirational."

Dr. A. Metin Gülmezoglu
Department of Reproductive Health and Research
World Health Organization

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Introduction

Introduction

This publication marks 18 years since the Effective Care Research Unit opened its office in East London and became part of the East London Hospital Complex.

About ECRU

The Effective Care Research Unit (ECRU) is a clinical research unit that specializes in reproductive health research. It was first established at the University of the Witwatersrand (Wits), Johannesburg, in 1988 and was transferred to East London in 2000, where it functions as a collaboration between Wits University, Walter Sisulu University, the University of Fort Hare, and the Eastern Cape's Department of Health.

ECRU's move to East London was a strategic one, to ensure that the Unit's research remained relevant to the needs of health workers and health service users in the most resource-poor parts of the country, to decentralize research activity and clinical expertise, and to ensure capacity-building in terms of research and clinical skills in the Eastern Cape region. Based in the Obstetrics and Gynaecology Department of the East London Hospital Complex, the principal objective of the ECRU is to promote evidence-based affordable care, appropriate to the needs of low-income communities.

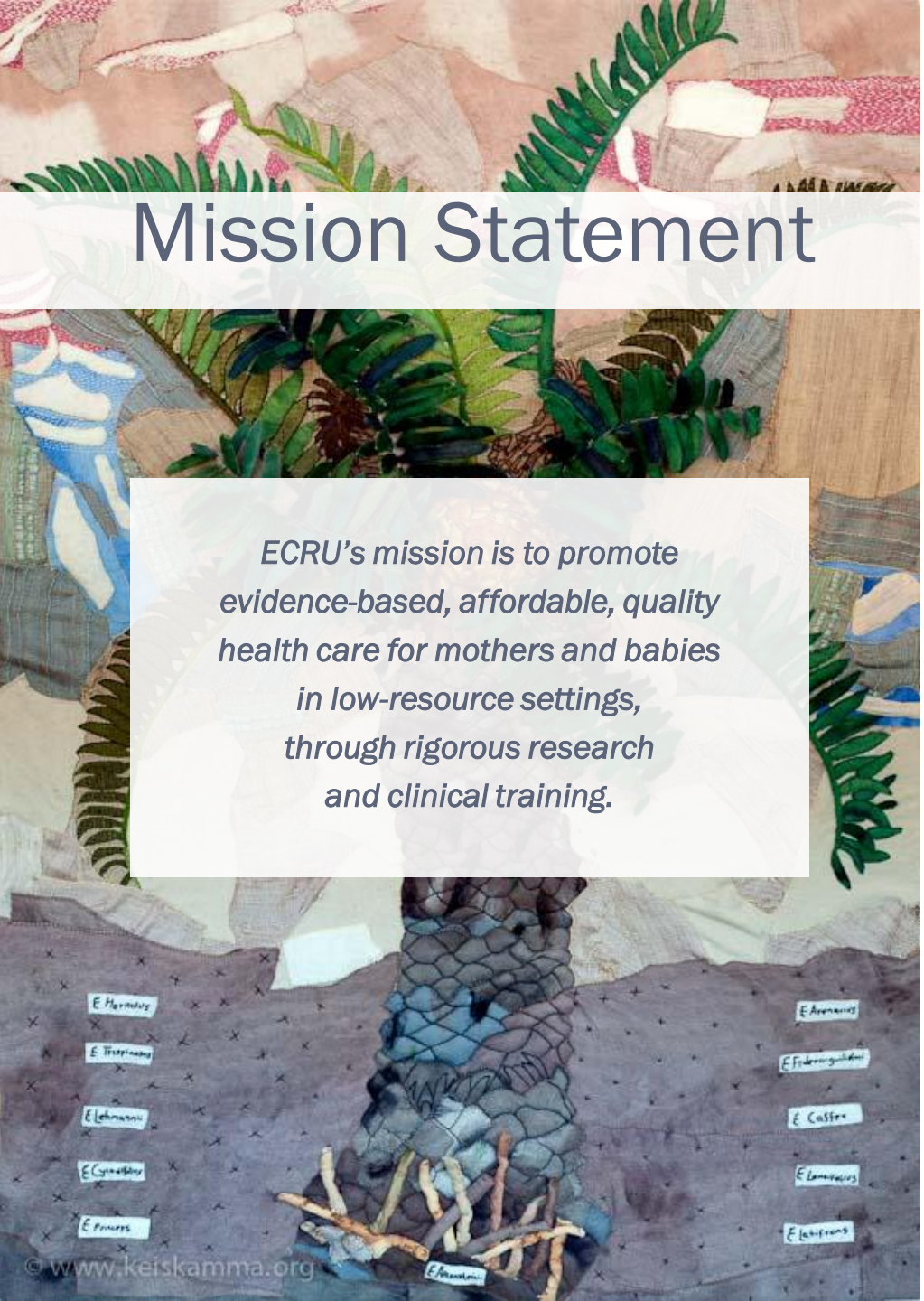
Principle activities include conducting systematic reviews, randomized trials, and evidence-based health care workshops. Research foci include hypertensive disorders of pregnancy, postpartum haemorrhage, effects of different contraception methods, and the prevention of mother-to-child transmission of HIV, among others.

Since 2001, the Unit has held annual Research Methods courses which have been highly rated by participants, several of whom have gone on to publish Cochrane systematic reviews and conduct clinical trials, often with ongoing mentoring from the ECRU staff.

In partnership with the Eastern Cape's Department of Health and the University of Fort Hare, the Unit has successfully implemented the Better Births Initiative (BBI) to promote humane and evidence-based child birth in hospitals in the Eastern Cape.

ECRU has brought significant international research funding into the Eastern Cape, and is accredited as a World Health Organization (WHO) Collaborating Centre in Reproductive Health Research Synthesis.

Mission Statement



ECRU's mission is to promote evidence-based, affordable, quality health care for mothers and babies in low-resource settings, through rigorous research and clinical training.

Objectives

- To *conduct clinical trials* to address reproductive health problems that represent the greatest burden of disease.
- To *generate review evidence* from clinical trials through Cochrane Systematic Reviews.
- To *disseminate evidence* on reproductive health interventions that is appropriate to the needs, customs and constraints of low-income country populations.
- To *facilitate implementation* of evidence-based health care through clinical capacity strengthening workshops.
- To *develop research capacity* by training researchers, in particular midwives and doctors in research methodology.

Justus Hofmeyr

Founder and Director

Justus Hofmeyr graduated from the University of the Witwatersrand in 1973 and worked at the Holy Cross Mission Hospital in the former Transkei (Eastern Cape, South Africa). He published his first research paper during this time (1979) and went on to specialise in Obstetrics and Gynaecology, obtaining his MRCOG in 1980.

In 1988 he became Professor and Head of Obstetrics and Gynaecology at Coronation Hospital in Johannesburg, and first set up the ECRU. In 2000, Justus transferred with ECRU to the East London Hospital Complex to contribute to health care, research and capacity development in the Eastern Cape.

Justus has published some 340 peer-reviewed papers, 29 book chapters and nine audio-visual teaching videos. As a champion of evidence-based care, and in acknowledgement of his significant contribution to advancing medical knowledge and improving quality of care, Justus was honoured with the “Spirit of Medicine” award from the South African Medical Association in 2012. He received a Doctorate in Science degree from the University of the Witwatersrand in 2013.

With his wife Dr Carol Hofmeyr, he is also extensively involved with rural community development and outreach programmes through the Keiskamma Trust.

Important research contributions include:

- *Leading a research program that discovered the enduring effects of supportive companionship during childbirth*
- *Pioneering research on external cephalic version for breech presentation*
- *Conducting the first randomized trials of misoprostol for preventing postpartum haemorrhage, of delayed cord clamping for preterm birth, and of pre-pregnancy calcium supplementation for preventing pre-eclampsia;*
- *Titrating oral misoprostol solution for safe labour induction*
- *Developing a model for onsite midwife-led birth units*
- *Discovering “posterior axillary sling traction” for shoulder dystocia.*

Mandisa Singata-Madliki

Co-Director

Mandisa Singata-Madliki joined ECRU in 2001, after qualifying as a Registered Nurse from Ciskei Nursing College at Cecilia Makiwane Hospital (East London).

As a student, Mandisa's strong leadership skills and passion for her profession were already evident, acting as President of the Student Representative Council, the Eastern Cape Provincial Chairperson for the South African Student Nurse Organisation, and a member of the National Department of Health Nurse Curriculum Committee during this time.

In 2008, Mandisa was awarded her Masters of Business Administration degree from the Regent Business School (East London), and was promoted to the position of Deputy Director of ECRU. Through the support of ECRU, Mandisa studied towards a Doctor of Philosophy degree (PhD), which was awarded in 2014 from the University of Cape Town. She has been Co-Director of ECRU since 2016.

Mandisa has served as an expert on World Health Organization guideline development panels and is the South African representative for the International Mother Baby Childbirth Organization. On behalf of ECRU, she has collaborated with the Department of Health to improve health care in the Eastern Cape, through projects such as the Better Births Initiative, assisting with training workshops in all Eastern Cape districts.

Mandisa's responsibilities include organizing ECRU's research staff, coordinating ECRU's clinical trials and training workshops, managing ECRU's finances, and writing up and publishing research findings.

In 2015 she was awarded a 5-year Medical Research Council grant for the COHERE Project, and a major MRC research grant for the WHICH Part 1 Study.

The ECRU team

Effective Care Research Unit

Front row: Mandisa Mdingi (Research Midwife), Dr. Mandisa Singata-Madliki (Co-Director), Portia Mbada (Recruiter)
Middle row: Zodwa Fawule (Recruiter), Nomthandazo Monakali (Fieldworker), Xoliswa Manyisana (Counsellor), Dr. Joanne Batting (Research Doctor), Erica Mashalaba (Receptionist), Bulelwa Nogidela-Makhutha (Project Manager), Pumla Mlotana (Research Midwife), Thembeka Lekota (Retention Officer)

Back row: Mzwabantu Gqoboka (Driver), Prof. Justus Hofmeyr (Director), Mlungisi Mxesibe (Lab. Technologist), Paula Matross (Administrator), Nolukhanyo Madliki (Counsellor)

The ECRU team

Frere and Cecilia Makiwane Hospitals

Frere and Cecilia Makiwane Hospitals (previously known as the East London Hospital Complex) are government-funded Provincial referral hospitals. They are situated approximately 23 kilometres apart, with an average of 700 beds each.

The Cecilia Makiwane Hospital (CMH) is named after nursing pioneer Cecilia Makiwane, who was South Africa's first professional black African nurse, and an early activist in the struggle for women's rights. Facilities include a high care maternity ward and an antiretroviral clinic dedicated to adults and children with HIV/AIDS.

Frere Hospital is a key tertiary teaching hospital, renowned for its large, well-equipped maternity wing, Onsite Midwife-led Birth Unit (OMBU), and high-tech Neonatal Intensive Care Unit (NICU). In addition to maternity and HIV/AIDS services, the Obstetrics and Gynaecology Department at Frere Hospital includes specialized services such as foetal ultrasound, reproductive medicine, gynae-oncology and uro-gynaecology. In 2018, the International Hospital Federation recognized Frere Hospital for its turnaround quality improvement project.

Left: Celia Makiwane Charcoal on Paper, by Amitabh Mitra
Right: Cecelia Makiwane Hospital

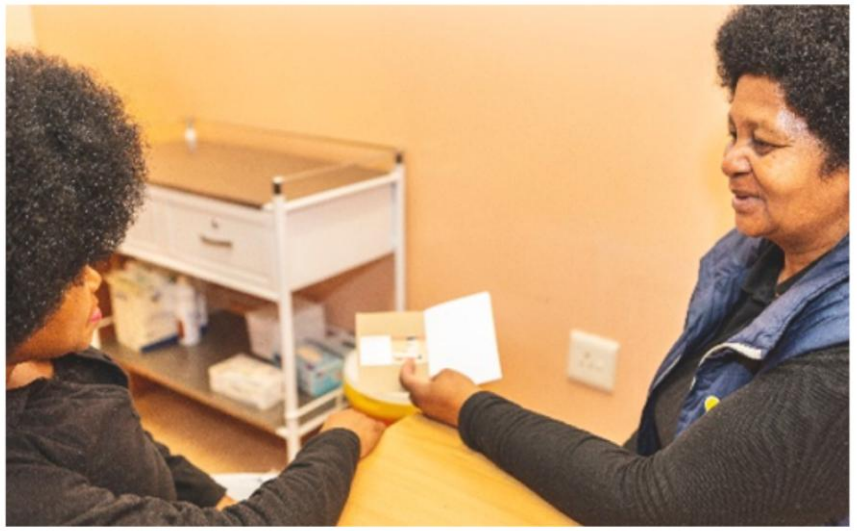
Frere Hospital

Research Spaces

ECRU recruits participants for most of its clinical trials from the Obstetrics and Gynaecology wards, clinics and the Onsite Midwife-led Birth Unit and therefore has offices and dedicated research space in both the Frere and Cecilia Makiwane Hospitals.

At Cecilia Makiwane Hospital, the ECRU research space comprises an office, reception area, waiting room, two clinical examination rooms, treatment room, and a kitchen.

At Frere Hospital, there are a further two offices, together with a clinical examination room, a minus 80° C freezer, and a back-up freezer.



Because the Frere OMBU is on site, it can more easily be included in research projects, and participation in research has a positive effect on staff motivation and quality of care.

The OMBU

The Onsite Midwife-led Birth Unit at Frere Hospital includes five delivery beds, six postnatal beds, and one newborn resuscitation station. It is currently staffed by birth care teams consisting of an operational manager, four midwives, a nurse, and a nursing assistant. Whilst being located within the hospital, care is midwife-led until the point of up-referral. This provides for comprehensive emergency obstetric and newborn care.

Service Users

The Eastern Cape Province is the third most populous province in South Africa (home to 7 million people), but remains the poorest, with a large proportion of the population living below the national poverty line, and severe socio-economic deprivation prevailing.

The majority of the population is rural (62%), with women comprising 53% of the total. There are very high rates of childbirth, especially amongst black Africans, rural women, and those with no formal education.

About 88% of the Eastern Cape population is serviced by the public health sector and, at Frere and Cecelia Makiwane Hospitals, services are free to pregnant and breastfeeding women, and children under the age of six years old.

Alongside maternity service providers, service users are ECRUs most important stakeholders, with the combined hospitals' maternity services facilitating approximately 13 000 births per annum. Hypertension in pregnancy is the most prevalent pregnancy complication among its users. However, HIV/AIDS indirectly contributes significantly to maternal and perinatal morbidity and mortality, due to its high prevalence among antenatal women in the Eastern Cape - around 30.2%.[1]

[1] National Antenatal Sentinel HIV & Syphilis Report (2015).

In addition, unplanned, teenage pregnancy is the highest in the Eastern Cape of all the South African provinces, with almost 13% of births occurring among girls under the age of 18 (almost double the national average).

ECRU Stakeholders

ECRU is a formal research unit of the University of Witwatersand (Wits), and submits protocols to their internationally and Good Clinical Practice compliant ethics committee. ECRU has also collaborated with other Wits research units such as the Match Research Unit and the Wits Reproductive Health and HIV Institute. The latest review of the ECRU by Wits is until the end of 2019.

The ECRU Director (Justus Hofmeyr) is on a joint appointment between the Department of Health (DOH) and Walter Sisulu University as a consultant/professor. All DOH service users are linked to Walter Sisulu University and the ECRU recruits research volunteers from them.

ECRU established a memorandum of understanding with the University of Fort Hare (UFH) in 2002, and UHF is currently responsible for ECRU financial administration and Human Resources.

ECRU is a collaborating centre for the World Health Organization for research synthesis in Reproductive Health and has benefited from a Long-term Institutional Development Grant for approximately three terms.

ECRU Community Advisory Board

The Community Advisory Board serves as a vital link between the community and ECRU.

Capacity Building

Clinical Strengthening

The Better Births Initiative (BBI) is a global initiative calling for improved childbirth care for women, principally developed by the Effective Care Research Unit, in collaboration with Liverpool School of Tropical Medicine and the Reproductive Health Research Unit.

The BBI involves a workshop-based intervention to promote humane and evidence-based care for women during childbirth, especially in low-income countries.

It has been implemented opportunistically in South Africa, and ECRU has developed partnerships throughout the Eastern Cape, with the Maternal and Child Health Directorate and the Department of Nursing Science, Fort Hare, to promote “Better Births” in the province.

In 2002, ECRU conducted BBI workshops in all 24 districts of the Eastern Cape, and these were followed up in all regions in 2003. These workshops included a wide range of participants, for example, the BBI workshop at Mowbray Hospital in 2002 was attended by midwives from all Midwife Obstetric Units and hospitals, obstetricians, registrars, and medical superintendents.

Capacity Building

Research Capacity Strengthening

Mandisa Singata-Madliki (PhD, 2014)

Bulelwa Nogidela-Makhutha (Basic, Intermediate and Advanced Project Management, 2017)

Nolusindo Yonto (Masters, 2018)

A principle objective of ECRU is to develop research capacity by training researchers, in particular, doctors and midwives, in research conduct and methodology.

Staff development

ECRU is actively involved in furthering the academic development of its own staff. An example of this is in ECRU's financial and academic support provided to Mandisa Singata-Madliki (now ECRU's Co-Director) towards her Masters in Business Administration degree in 2008 and her PhD degree in 2014.

Other examples include our Project Manager, Bulelwa Nogidela-Makhutha, who completed a Learning Programme in Basic, Intermediate and Advanced Project Management through UNISA in 2017, and ECRU Research Midwife, Nolusindiso Yonto, who obtained her Masters in Nursing degree in 2018.

ECRU has also supported several other nurses and doctors towards obtaining their Masters and PhD qualifications and, to date, Justus Hofmeyr has supervised eight successful PhD candidates.

Good Clinical Practice Training

ECRU is committed to ensuring that affiliated students and other researchers embarking on clinical research are fully aware of their responsibilities to conduct research that is ethical. Therefore, in addition to running annual Research Methods Courses, ECRU provides guidance on the design, conduct, performance, monitoring, recording and reporting of research studies, through running regular Good Clinical Practice (GCP) Training Courses.

These GCP courses are specifically designed to protect the research subjects and to validate data, with a strong emphasis on Research Ethics.

Research Capacity Strengthening

Research Methods Courses

ECRU has run annual Research Methods Course Workshops since 2001, attended by over 300 prospective researchers from South Africa and other African countries.

Partly funded by World Health Organization (WHO), the workshops equip participants with the knowledge and skills to plan, conduct, analyse and publish a randomized clinical trial, following Good Clinical Practice guidelines.

In addition, participants are mentored in how to conduct a systematic review of randomized trials for publication in the Cochrane Library, and are trained in the use of Review Manager, Epi-info, Excel and WHO Reproductive Health Library software.

The Research Methods Course Workshops have been highly appreciated and commended by the participants, as is evident from correspondence received by ECRU after the courses.

Hi Prof, I hope I find you in good health. I would like to take this opportunity to thank you for granting me the opportunity to attend the Research Methods Training Course in randomized controlled trials and systematic reviews. Due to its hands on and practical approach the course really helped me with the skills and knowledge on how to conduct randomized controlled trials and systematic reviews. I hope to use the skills and knowledge gained in improving the health and well being of people in my community and country. I also hope to use the skills and knowledge gained in my further studies as I am in the process of starting a PHD. The course was well organized. It took you much commitment and dedication to organize such an excellent training. My special gratitude to you and the entire ECRU team for organizing a fantastic training. Thank you Prof

Kind Regards

Fungai Mbengo

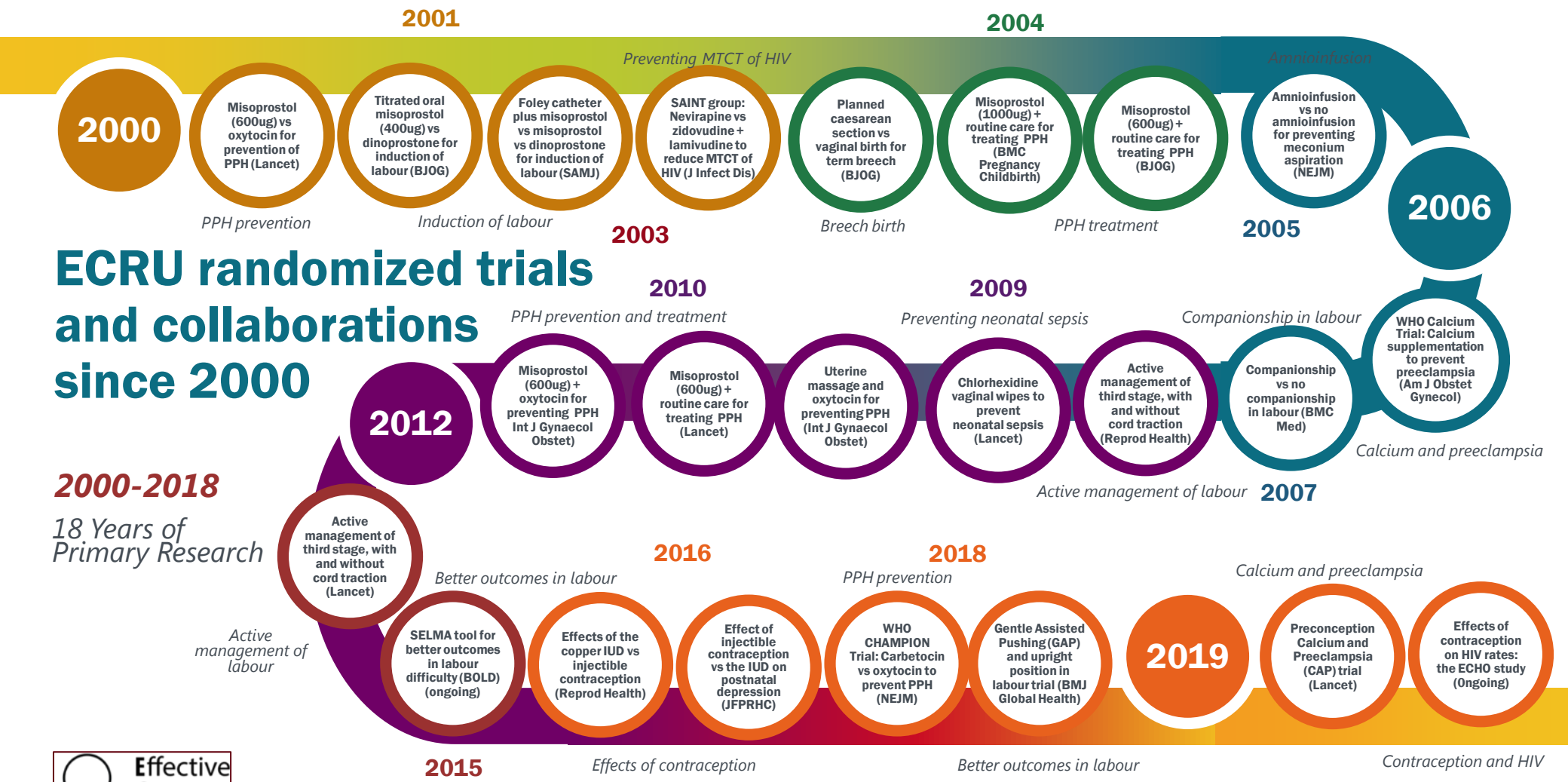
Dear Carol
Thank you very much for the results. I had a wonderful time at East London. Thanks for the wonderful opportunity you gave me to be a part of this prestigious course.
We will stay in touch as one big family
Sincerely
Dr Frederick Morfaw M.D. MSc (Edinburgh-UK), CB/GYN (FMBS Yaounde)

Dear Mandisa, Carol and Prof. Hofmyer, Many many many thanks!!
Just to say how thankful I am and how reminescence I am of the experience and training. I must say, in addition to many other things, I am thankful for my near the window sitting position during most of the flights. I discovered more than I could anticipate. I hope you will be seeing my name in the papers in the near future as a product of your sacrificial hardwork and investment in the next generation.
I am the young investigator from Cameroon, working with a Catholic hospital in rural Nguti and working for now as a freelance researcher.
Lots of love,
Arnold Fru-Mukete, M.D (FHS, University of Buea, Cameroon)
St. John of God Hospital, Nguti, Cameroon

A sample of feedback received after the 2014 Research Methods Course Workshop

Research Focus

Overview of ECRU trials since 2000: 18 years of scientific excellence



ECRU randomized trials and collaborations since 2000

2000-2018

18 Years of Primary Research

Effective Care Research Unit

Postpartum Haemorrhage

Postpartum haemorrhage (PPH) is a leading cause of maternal death worldwide, and is defined as blood loss greater or equal to 500ml following vaginal birth, or 1000 ml following caesarean section within the first 24 hours of birth. The standard practice to reduce excessive bleeding at childbirth is the administration of a uterotonic drug to contract the uterus. Oxytocin is widely considered the drug of choice, but it requires cold storage, which is not available in many settings.

A country's maternal death rate from PPH is a fair indication of how well a country's health system is functioning, as PPH tests timely referral, available supplies, and the number and skills of health workers. In the *Seventh Trienniel Report on Confidential Enquiries into Maternal Deaths in South Africa (2017),* haemorrhage was the third most common cause of maternal death for the triennium 2014 to 2016.

Tragically, over 80% of PPH deaths were identified as "clearly avoidable", with sub-standard care remaining a major problem, and many deaths occurring in out-of-hospital settings, with injectable uterotonics seldom available.

Photo: Courtesy of The Keiskamma Trust

Alternative options to injectable oxytocin for PPH prevention and treatment are needed. It is within this context that the ECRU has contributed vital knowledge concerning alternative methods for the prevention and treatment of PPH, such as misoprostol, carbetocin, uterine massage and the use of the uterine balloon tamponade and uterine suction tamponade.

Primary research

Misoprostol for PPH prevention

Misoprostol is an inexpensive and stable prostaglandin E1 analogue, and the administration of this drug at a community level to prevent and treat PPH has been shown to be important when other uterotonic agents are not available. ECRU's Director was an early instigator of research efforts to investigate its effectiveness in PPH management, and ECRU has been instrumental in producing the primary evidence to define its use.

The first ever randomized trial of misoprostol to prevent PPH was conducted by ECRU in 1995, when it was still based in Johannesburg, and evaluated the effect of 400 µg oral misoprostol compared with an identical placebo on postpartum blood loss (*Hofmeyr et al, 1998*). The potential shown by misoprostol to reduce PPH in this early double-blind ECRU trial led to the conduct of many more trials to evaluate its effectiveness in preventing PPH.

ECRU subsequently participated in the large WHO collaborative trial, along with investigators in Argentina, China, Egypt, Ireland, Nigeria, South Africa, Switzerland, Thailand, and Vietnam, to compare 600 µg oral misoprostol with oxytocin (10IU IM or IV) among 18,530 women. Findings from this trial, reported in *The Lancet* in 2001, showed that oxytocin was preferable to misoprostol when used for PPH prevention (*Gülmezoglu et al, 2001*).

Table 2
Outcomes of the trial.[a]

Outcomes	Misoprostol		Placebo		RR/WMD (95% CI) [b]
Primary	n		n		
Blood loss≥500 mL within 1 h after taking trial tablets	546	22 (4.0)	553	35 (6.3)	0.64 (0.38–1.07)
Secondary					
Mean blood loss within 1 h after taking trial tablets, mL	540	189	549	199	−9.58 (−22.3 to 3.14)
Blood loss≥1000 mL within 1 h after taking trial tablets	546	5 (0.9)	553	1 (0.2)	3.70 (0.61–22.38)
Mild shivering	544	142 (25.6)	556	67 (12.1)	2.14 (1.25–3.70)
Moderate to severe shivering	377	30 (8.0)	381	13 (3.4)	2.34 (1.25–4.39)
Pyrexia≥37.5 °C	522	61 (11.7)	536	28 (5.2)	2.24 (1.48–3.41)
Pyrexia≥39 °C	521	8 (1.5)	536	1 (0.2)	2.60 (0.05–136.8)
Manual removal of placenta	446	32 (7.2)	455	33 (7.3)	0.98 (0.62–1.55)
Laparotomy	546	4 (0.7)	556	5 (0.9)	N/A
Hysterectomy	546	1 (0.2)	557	0 (0.0)	N/A
Severe maternal morbidity or death	546	4 (0.7)	557	5 (0.9)	N/A
Maternal death	546	0 (0.0)	557	0 (0.0)	N/A

Abbreviations: CI, confidence interval; RR, relative risk; WMD, weighted mean difference.
[a] Values are given as number (percentage) unless otherwise indicated.
[b] Derived from meta-analysis of the results from the different sites.
[c] I2 indicates heterogeneity between the sites

Following on from this important research, the East London-based ECRU undertook another misoprostol trial involving four sites and 1,103 women in Nigeria, South Africa and Uganda (*Hofmeyr et al, 2011*). The trial was supported by Gynuity Health Projects in New York, USA, and the aim was to evaluate whether misoprostol added to oxytocin was more effective than oxytocin alone for the active management of the third stage of labour.

In this double-blind placebo-controlled trial, 400 µg of misoprostol or placebo was administered sublingually, in addition to the standard 10IU of oxytocin. The trial findings suggested a potential modest benefit of 400 µg misoprostol, consistent with other published studies; however, they also highlighted the increased risk of unpleasant side effects, like fever and shivering with misoprostol.

Research Focus: Postpartum Haemorrhage

Rose Altar Piece Tapestry (Photo: courtesy of The Keiskamma Trust)

Primary research

Carbetocin for PPH prevention

To help to evaluate a heat-stable version of carbetocin, ECRU contributed to a large WHO multi-centre, randomized trial between July 2015 and January 2018. The trial involved 29,645 women in 10 countries (Argentina, Egypt, India, Kenya, Nigeria, Singapore, South Africa, Thailand, Uganda, and the United Kingdom) and compared intramuscular (IM) carbetocin (100 µg) with standard care (oxytocin 10IU IM), administered immediately after vaginal birth.

The research concluded that heat-stable carbetocin was of similar effectiveness (non-inferior) to oxytocin with regard to the use of additional uterotonic agents, and for the prevention of PPH (blood loss of at least 500 ml). Non-inferiority could not be shown for the outcome of blood loss of at least 1000 ml, due to low event rates for this outcome.

These findings are of crucial significance for the care of women in countries such as South Africa, where a lack of cold storage could act as a barrier to the prevention of PPH with oxytocin.

This trial was supported by Merck Sharpe & Dohme [MSD]) through the MSD for Mothers Program.

Research Focus: Postpartum Haemorrhage

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CLINICAL ARTICLE

Administration of 400 μg of misoprostol to augment routine active management of the third stage of labor

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ABSTRACT

Objective: To assess the effectiveness and safety of the administration of misoprostol, an orally active prostaglandin, in addition to routine uterotonic therapy as part of the active management of the third stage of labor. *Methods:* The present study was a hospital-based, decentralized, multi-center, randomized, placebo-controlled, double-blind trial. We enrolled 1103 women (out of a target sample size of 1180) at 4 hospitals in South Africa, Uganda, and Nigeria. Participants received a sublingual dose of 400 μg of misoprostol or a placebo, in addition to standard active management of the third stage of labor, after vaginal birth. *Results:* The baseline characteristics of the participants were comparable. The difference in the primary outcome of blood loss of 500 mL or more within 1 hour of randomization was not significant between the 2 groups (misoprostol 22/546 [4.0%] versus placebo 35/553 [6.3%]; relative risk, 0.64; 95% confidence interval, 0.38–1.07). Shivering and pyrexia occurred more frequently in the misoprostol group. No maternal deaths occurred. *Conclusion:* The present study did not confirm a beneficial effect of administering 400 μg of misoprostol, in addition to routine uterotonic therapy, during the third stage of labor, but was consistent with other trials showing a cumulative modest benefit. Where routine uterotonics are available for prophylactic use, any potential benefit of misoprostol might not outweigh the likelihood of adverse effects. Trial registered on clinical trials.gov: NCT 00124540.

1. Introduction

Postpartum hemorrhage (PPH) is the main cause of maternal mortality in many low-income countries, causing an estimated 125 000 deaths per year [1]. In a community-based study in Senegal, estimates of maternal mortality in 3 regions ranged from 436 to 852 per 100 000 live births [2]. Two-thirds of the deaths were directly due to obstetric causes, with the most common being hemorrhage [2]. In the UK, the risk of maternal death from hemorrhage is approximately 1 in 100 000 births [3]. The potential to save mothers' lives with medical interventions for hemorrhage is, thus, considerable.

There is evidence that a policy of active management of the third stage of labor [4] and 1 component of active management—namely, the routine administration of uterotonic drugs such as oxytocin [5], ergometrine [6], or both [7]—are effective in reducing the risk of PPH.

Systematic review has shown that coupling ergometrine treatment with oxytocin treatment in the active management of the third stage increases effectiveness, but with considerable adverse effects [7]. There is a sound biologic basis for expecting that misoprostol might similarly augment the effectiveness of injectable uterotonics. Misoprostol is a methyl ester (a synthetic analog) of the natural prostaglandin E1. It is marketed and registered for use in the prevention and treatment of peptic ulcer disease caused by prostaglandin synthetase inhibitors. It is a thermostable drug, can be administered with ease, and is relatively inexpensive.

Oral, sublingual, and rectal misoprostol treatments have been used for routine management of the third stage of labor. Several small trials have produced conflicting results. The main adverse effects, which are dose-dependent, are shivering and pyrexia [8]. In a large WHO collaborative trial of misoprostol in management of the third stage of labor [9], blood loss of more than 1000 mL and the use of additional oxytocics (the primary outcomes in the trial) occurred more frequently with misoprostol than with 10 units of oxytocin, indicating that oxytocin should remain the drug of choice for routine PPH prophylaxis.

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ORIGINAL ARTICLE

Heat-Stable Carbetocin versus Oxytocin to Prevent Hemorrhage after Vaginal Birth

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ABSTRACT

BACKGROUND
Postpartum hemorrhage is the most common cause of maternal death. Oxytocin is the standard therapy for the prevention of postpartum hemorrhage, but it requires cold storage, which is not available in many countries. In a large trial, we compared a novel formulation of heat-stable carbetocin with oxytocin.

METHODS
We enrolled women across 23 sites in 10 countries in a randomized, double-blind, noninferiority trial comparing intramuscular injections of heat-stable carbetocin (at a dose of 100 μg) with oxytocin (at a dose of 10 IU) administered immediately after vaginal birth. Both drugs were kept in cold storage (2 to 8°C) to maintain double-blinding. There were two primary outcomes: the proportion of women with blood loss of at least 500 ml or the use of additional uterotonic agents, and the proportion of women with blood loss of at least 1000 ml. The noninferiority margins for the relative risks of these outcomes were 1.16 and 1.23, respectively.

RESULTS
A total of 29,645 women underwent randomization. The frequency of blood loss of at least 500 ml or the use of additional uterotonic agents was 14.5% in the carbetocin group and 14.4% in the oxytocin group (relative risk, 1.01; 95% confidence interval [CI], 0.95 to 1.06), a finding that was consistent with noninferiority. The frequency of blood loss of at least 1000 ml was 1.51% in the carbetocin group and 1.45% in the oxytocin group (relative risk, 1.04; 95% CI, 0.87 to 1.25), with the confidence interval crossing the margin of noninferiority. The use of additional uterotonic agents, interventions to stop bleeding, and adverse effects did not differ significantly between the two groups.

CONCLUSIONS
Heat-stable carbetocin was noninferior to oxytocin for the prevention of blood loss of at least 500 ml or the use of additional uterotonic agents. Noninferiority was not shown for the outcome of blood loss of at least 1000 ml; low event rates for this outcome reduced the power of the trial. (Funded by Merck Sharpe & Dohme; CHAMPION Australian New Zealand Clinical Trials Registry number, ACTRN12614000870651; EudraCT number, 2014-004445-26; and Clinical Trials Registry–India number, CTRI/2016/05/006969.)

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*A complete list of investigators in the WHO CHAMPION Trial Group is provided in the Supplementary Appendix, available at NEJM.org.

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Research Focus: Postpartum Haemorrhage

Primary research

Misoprostol for PPH treatment

Research on misoprostol for PPH prevention led to the conduct of several studies to evaluate its effectiveness and safety in treating PPH. The first randomized, double-blind, placebo-controlled trial on misoprostol for PPH treatment (in addition to standard uterotonic agents, i.e. oxytocin 10IU IM or IV) was coordinated by ECRU and conducted at four South African Hospitals (Frere, Cecelia Makiwane, Tembisa and Chris Hani Baragwanath Hospitals) (*Hofmeyr et al, 2004*).

The trial was supported by the World Health Organization's Department of Reproductive Health and Research. The effect of misoprostol on additional blood loss was not statistically significant, however, the trial was underpowered and a significant effect could not be excluded.

These findings prompted the conduct of a large WHO multi-centre, placebo-controlled trial (Argentina, Egypt, South Africa, Thailand, Vietnam) between July 2005 and August 2008 to evaluate the effects of 600 µg sublingual misoprostol for PPH treatment, in addition to standard uterotonic agents (*Widmer et al, 2010*). Findings from this trial, which enrolled 1,422 women with PPH, showed that misoprostol provided no additional benefit over the standard PPH treatment.

ECRU played an active role in this trial, which was funded by the Bill & Melinda Gates Foundation, and UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction.

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Misoprostol for treating postpartum haemorrhage: a randomized controlled trial [ISRCTN72263357]

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Abstract

Background: Postpartum haemorrhage remains an important cause of maternal death despite treatment with conventional therapy. Uncontrolled studies and one randomised comparison with conventional oxytocics have reported dramatic effects with high-dose misoprostol, usually given rectally, for treatment of postpartum haemorrhage, but this has not been evaluated in a placebo-controlled trial.

Methods: The study was conducted at East London Hospital Complex, Tembisa and Chris Hani Baragwanath Hospitals, South Africa. Routine active management of the third stage of labour was practised. Women with more than usual postpartum bleeding thought to be related to inadequate uterine contraction were invited to participate, and to sign informed consent. All routine treatment was given from a special 'Postpartum Haemorrhage Trolley'. In addition, participants who consented were enrolled by drawing the next in a series of randomised treatment packs containing either misoprostol 5 × 200 μg or similar placebo, which were given 1 orally, 2 sublingually and 2 rectally.

Results: With misoprostol there was a trend to reduced blood loss ≥500 ml in 1 hour after enrolment measured in a flat plastic 'fracture bedpan', the primary outcome (6/117 vs 11/120, relative risk 0.56; 95% confidence interval 0.21 to 1.46). There was no difference in mean blood loss or haemoglobin level on day 1 after birth < 6 g/dl or blood transfusion. Side-effects were increased, namely shivering (63/116 vs 30/118; 2.14, 1.50 to 3.04) and pyrexia > 38.5°C (11/114 vs 2/118; 5.69, 1.29 to 25). In the misoprostol group 3 women underwent hysterectomy of whom 1 died, and there were 2 further maternal deaths.

Conclusions: Because of a lower than expected incidence of the primary outcome in the placebo group, the study was underpowered. We could not confirm the dramatic effect of misoprostol reported in several unblinded studies, but the results do not exclude a clinically important effect. Larger studies are needed to assess substantive outcomes and risks before misoprostol enters routine use.

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

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Summary

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

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

Findings 1422 women were assigned to receive misoprostol (n=705) or placebo (n=717). The proportion of women with blood loss of 500 mL or more within 60 min was similar between the misoprostol group (100 [14%]) and the placebo group (100 [14%]; relative risk 1·02, 95% CI 0·79–1·32). In the first 60 min, an increased proportion of women on misoprostol versus placebo, had shivering (455/704 [65%] *vs* 230/717 [32%]; 2·01, 1·79–2·27) and body temperature of 38°C or higher (303/704 [43%] *vs* 107/717 [15%]; 2·88, 2·37–2·50).

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

Funding Bill & Melinda Gates Foundation, and UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction.

Introduction

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

Misoprostol is a prostaglandin E1 analogue that is widely marketed in tablet form, and is registered for use in the prevention and treatment of peptic ulcer disease. It is thermostable, can be taken orally, and is fairly inexpensive. Although misoprostol is less effective than oxytocin for prevention of post-partum haemorrhage,[4] it has been promoted widely for the ease with which the drug can be taken,[5] and the positive results from a trial of misoprostol administration by rural birth attendants in India.[6] Concerns about misuse[7] and side-effects[8] have emerged, and misoprostol use for labour induction seems to increase post-partum blood loss.[9]

Clinical use of misoprostol for post-partum haemorrhage is based on weak evidence.[10,11] At the start of our study, three randomised trials of misoprostol for treatment of post-partum haemorrhage had been published.[12–14] Lokugamage and colleagues[12] reported that 800 μg rectal misoprostol stopped post-partum haemorrhage significantly more effectively than did combined intramuscular syntometrine and intravenous syntocinon. However, in that trial treatment allocation was unblinded and the outcome was subjective assessment of clinical response, so investigator bias could have favoured the misoprostol group. Hofmeyr[13] and Walraven[14] and their colleagues did double-blind trials and showed reduced blood loss with misoprostol compared with placebo, both in combination with standard uterotonics, but the differences were not significant. In a meta-analysis of the results of these trials, misoprostol significantly reduced the primary outcome of additional blood loss of 500 mL or more (relative risk 0·57, 95% CI 0·34–0·96).[15] However, in a systematic review, Mousa and Alfirevic[16] concluded that evidence for any advantage from

Research Focus: Postpartum Haemorrhage

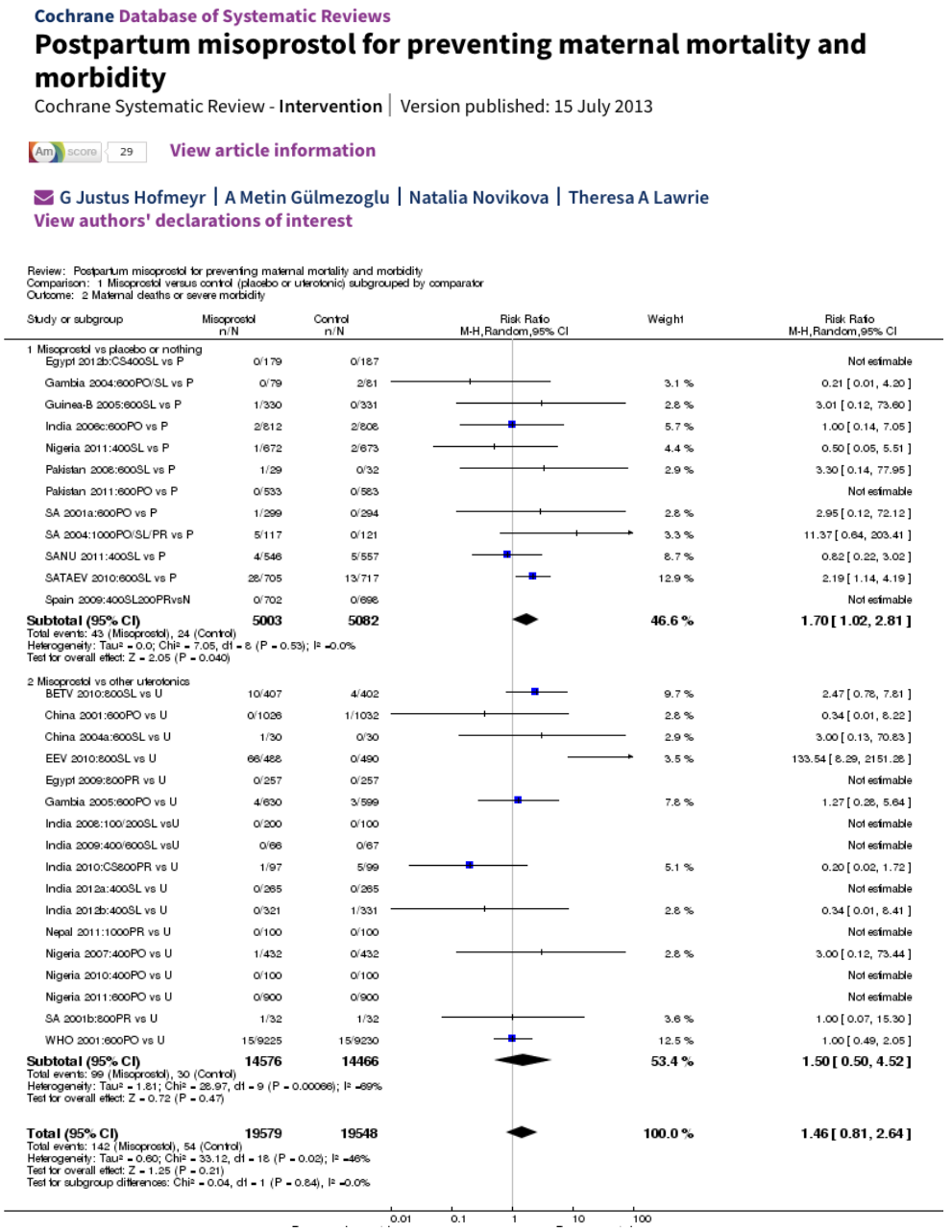
Evidence synthesis

Misoprostol for preventing maternal mortality and morbidity

In 2009 and 2011, Justus Hofmeyr and colleagues conducted systematic reviews to evaluate the evidence on misoprostol for PPH prevention and treatment. The 2011 review was a Cochrane systematic review, which was updated in 2013. A total of 78 RCTs were included in the update, with more than 59,000 participants contributing data to the review (*Hofmeyr et al, 2013*).

These reviews found that misoprostol increased the composite outcome 'maternal morbidity and mortality' compared with placebo or nothing, and was not as effective as standard care (oxytocin 10IU) for PPH prevention. Pyrexia (fever) was found to be commonly associated with misoprostol use; however, a dose of 400 µg was as effective as higher doses and was associated with a lower risk of side effects.

The reviews concluded that due to the enormous need for an effective oral uterotonic such as misoprostol, the latter could potentially be used on a large scale with ongoing monitoring and evaluation. However, the use of misoprostol should not detract from international efforts to ensure that all childbearing women have access to conventional uterotonics that have been proven safe and effective.



Cochrane Database of Systematic Reviews

Postpartum misoprostol for preventing maternal mortality and morbidity

Cochrane Systematic Review - **Intervention** | Version published: 15 July 2013

Am score 29 View article information

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View authors' declarations of interest

Review: Postpartum misoprostol for preventing maternal mortality and morbidity
Comparison: 1 Misoprostol versus control (placebo or uterotonic) subgrouped by comparator
Outcome: 2 Maternal deaths or severe morbidity

Study or subgroup	Misoprostol n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Misoprostol vs placebo or nothing					
Egypt 2012b:CS400SL vs P	0/179	0/187			Not estimable
Gambia 2004:600PO/SL vs P	0/79	2/81		3.1 %	0.21 [0.01, 4.20]
Guinea-B 2005:600SL vs P	1/330	0/331		2.8 %	3.01 [0.12, 73.60]
India 2006c:600PO vs P	2/812	2/808		5.7 %	1.00 [0.14, 7.05]
Nigeria 2011:400SL vs P	1/672	2/673		4.4 %	0.50 [0.05, 5.51]
Pakistan 2008:600SL vs P	1/29	0/32		2.9 %	3.30 [0.14, 77.95]
Pakistan 2011:600PO vs P	0/533	0/583			Not estimable
SA 2001a:600PO vs P	1/299	0/294		2.8 %	2.95 [0.12, 72.12]
SA 2004:1000PO/SL/PR vs P	5/117	0/121		3.3 %	11.37 [0.64, 203.41]
SANU 2011:400SL vs P	4/546	5/557		8.7 %	0.82 [0.22, 3.02]
SATAEV 2010:600SL vs P	28/705	13/717		12.9 %	2.19 [1.14, 4.19]
Spain 2009:400SL200PRvsN	0/702	0/698			Not estimable
Subtotal (95% CI)	**5003**	**5082**		**46.6 %**	**1.70 [1.02, 2.81]**
Total events: 43 (Misoprostol), 24 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 7.05, df = 8 (P = 0.53); I² =0.0%					
Test for overall effect: Z = 2.05 (P = 0.040)					
2 Misoprostol vs other uterotonics					
BETV 2010:600SL vs U	10/407	4/402		9.7 %	2.47 [0.78, 7.81]
China 2001:600PO vs U	0/1026	1/1032		2.8 %	0.34 [0.01, 8.22]
China 2004a:600SL vs U	1/30	0/30		2.9 %	3.00 [0.13, 70.83]
EEV 2010:600SL vs U	66/488	0/490		3.5 %	133.54 [8.29, 2151.28]
Egypt 2009:800PR vs U	0/257	0/257			Not estimable
Gambia 2005:600PO vs U	4/630	3/599		7.8 %	1.27 [0.28, 5.64]
India 2008:100/200SL vsU	0/200	0/100			Not estimable
India 2009:400/600SL vsU	0/66	0/67			Not estimable
India 2010:CS800PR vs U	1/97	5/99		5.1 %	0.20 [0.02, 1.72]
India 2012a:400SL vs U	0/265	0/265			Not estimable
India 2012b:400SL vs U	0/321	1/331		2.8 %	0.34 [0.01, 8.41]
Nepal 2011:1000PR vs U	0/100	0/100			Not estimable
Nigeria 2007:400PO vs U	1/432	0/432		2.8 %	3.00 [0.12, 73.44]
Nigeria 2010:400PO vs U	0/100	0/100			Not estimable
Nigeria 2011:600PO vs U	0/900	0/900			Not estimable
SA 2001b:800PR vs U	1/32	1/32		3.6 %	1.00 [0.07, 15.30]
WHO 2001:600PO vs U	15/9225	15/9230		12.5 %	1.00 [0.49, 2.05]
Subtotal (95% CI)	**14576**	**14466**		**53.4 %**	**1.50 [0.50, 4.52]**
Total events: 99 (Misoprostol), 30 (Control)					
Heterogeneity: Tau² = 1.81; Chi² = 28.97, df = 9 (P = 0.00086); I² =69%					
Test for overall effect: Z = 0.72 (P = 0.47)					
Total (95% CI)	**19579**	**19548**		**100.0 %**	**1.46 [0.81, 2.64]**
Total events: 142 (Misoprostol), 54 (Control)					
Heterogeneity: Tau² = 0.60; Chi² = 33.12, df = 18 (P = 0.02); I² =46%					
Test for overall effect: Z = 1.25 (P = 0.21)					
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² =0.0%					

0.01 0.1 1 10 100

Evidence synthesis

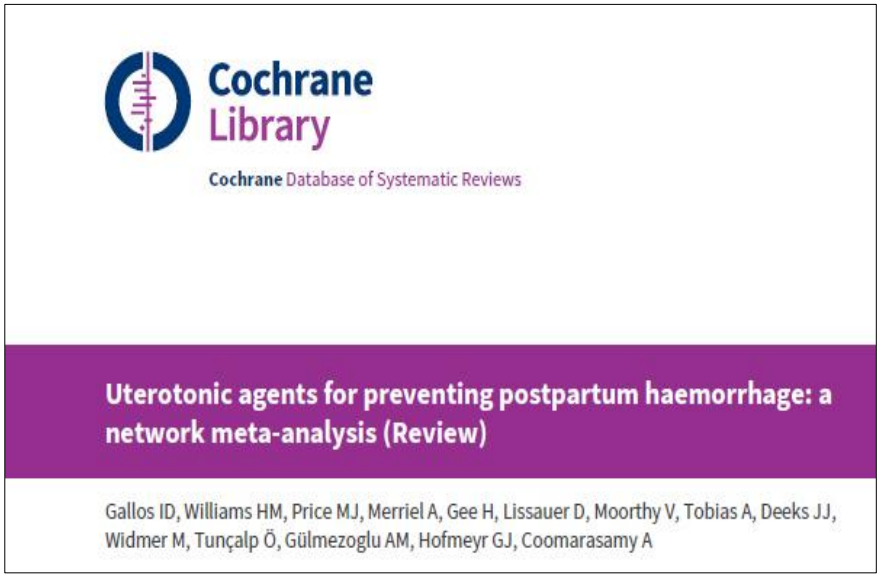
Uterotonic agents for preventing PPH: a network meta-analysis

In 2018, ECRU's Director collaborated with international colleagues on a Cochrane systematic review, led by Ioannis Gallos (Birmingham, UK), to identify the most effective uterotonic drugs for preventing PPH, and to generate a ranking according to their effectiveness and side-effect profiles (*Gallos et al, 2018*).

The results suggested that 'ergometrine plus oxytocin', 'misoprostol plus oxytocin', and carbetocin are the most effective drugs for the prevention of excessive bleeding after childbirth. This finding has important significance as, to date, the standard drug to prevent PPH has been oxytocin.

Heat-stable carbetocin, the newest uterotonic agent, was found to have the least side effects among the top three drug options. A set of standardized PPH outcomes are being developed for incorporation in future updates of this review.

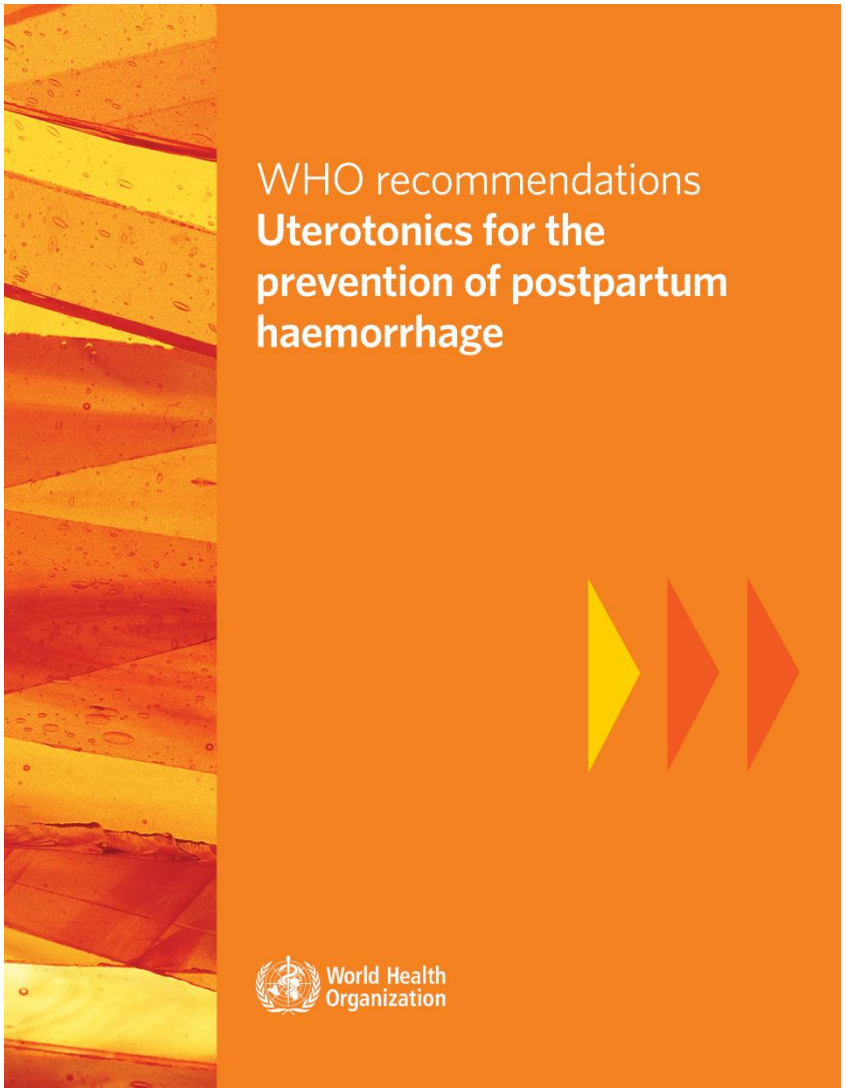
An associated cost-effectiveness review was conducted, entitled *"Uterotonic Drugs for the Prevention of Postpartum Haemorrhage: A cost-effectiveness Analysis" (2018*), the



objective of which was to estimate the relative cost-effectiveness for the full range of uterotonic drugs available.

Excluding adverse events, 'ergometrine plus oxytocin' was shown to be the least-costly strategy. This might be because the cost-effectiveness of uterotonic agents is largely driven by the drug supply price, and because misoprostol was considered to have costly side effects in the review's analysis model, which was based on the UK's health system.

Research Focus: Postpartum Haemorrhage



Research impact

The primary research conducted by ECRU, as well as the evidence syntheses collaborations have had a huge influence on the choice of uterotonic options to prevent and treat postpartum haemorrhage. Most recently, the resulting synthesized evidence has led to updated WHO recommendations for PPH prevention that should save lives.

WHO recommendations:

"The use of misoprostol (either 400 µg or 600 µg, PO) is recommended for the prevention of PPH for all births."

"The use of carbetocin (100 µg, IM/IV) is recommended for the prevention of PPH for all births in contexts where its cost is comparable to other effective uterotonics."

Source: WHO recommendations: Uterotonics for prevention of postpartum haemorrhage (2018)

Uterine balloon tamponade

Uterine balloon tamponade (UBT) refers to the general surgical principle of applying direct pressure to the site of haemorrhage, as a treatment for PPH, by means of various inflatable devices introduced into the uterine cavity.

A systematic review of non-randomized studies concluded that "UBT is an effective treatment for PPH in resource-poor settings", and as a result, UBT has become the focus of global programmes to reduce maternal deaths from PPH, with extensive implementation in low-income countries.

Justus Hofmeyr, in his 2017 paper entitled *"Time to test tamponade",* has called for high-quality research to evaluate it. However, he cautions that premature enthusiasm for promoting new interventions may do more harm than good, and proposes a large-scale, multinational randomized PPH treatment trial of UBT versus alternative care, in order to provide more robust evidence on which to base global programmes.

Primary research

Uterine massage to reduce PPH after vaginal birth

Between 2006 and 2009, ECRU, in collaboration with colleagues from Egypt, conducted a randomized controlled trial to determine the effectiveness of sustained uterine massage started before delivery of the placenta, to reduce postpartum haemorrhage (Abdel-Aleem et al, 2010).

The trial, which involved 1,964 women, showed that uterine massage alone was associated with more blood loss within 30 minutes after childbirth compared with treatment with oxytocin, with or without massage. Adding massage to oxytocin had no significant influence on blood loss after childbirth. These findings are consistent with a 2013 Cochrane systematic review.

Cochrane Library

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Uterine massage for preventing postpartum haemorrhage (Review)

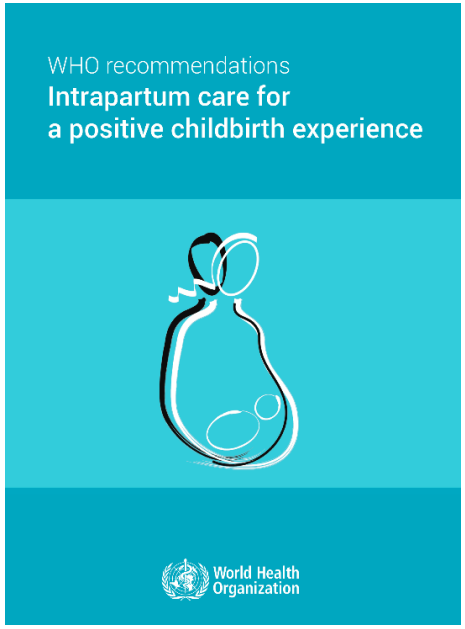
Hofmeyr GJ, Abdel-Aleem H, Abdel-Aleem MA

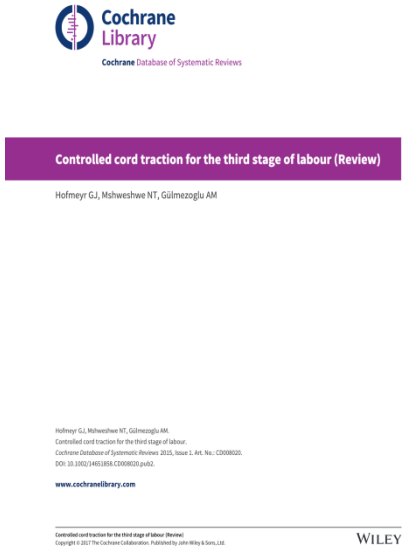
Research Focus: Postpartum Haemorrhage

Primary research

Controlled cord traction

Another large WHO trial, to which ECRU contributed, was the multi-centre randomized controlled trial on the active management of the third stage of labour, with and without controlled cord traction (CCT) (*Gülmezoglu et al, 2012*).This trial, conducted between June 2009 and Oct 2010, involving 24,390 women, showed that CCT could be omitted from management of the third stage as it had very little effect on the incidence of severe PPH. Evidence from this trial has impacted clinical guidelines.





Active management of the third stage of labour with and without controlled cord traction: a randomised, controlled, non-inferiority trial

A Metin Gülmezoglu, Pisake Lumbiganon, Sihem Landoulsi, Mariana Widmer, Hany Abdel-Aleem, Mario Festin, Guillermo Carroli, Zahida Qureshi, João Paulo Souza, Eduardo Bergel, Gilda Piaggio, Shivaprasad S Goudar, John Yeh, Deborah Armbruster, Mandisa Singata, Cristina Pelaez-Crisologo, Fernando Althabe, Peter Sekweyama, Justus Hofmeyr, Mary-Ellen Stanton, Richard Derman, Diana Elbourne

Summary

Background Active management of the third stage of labour reduces the risk of post-partum haemorrhage. We aimed to assess whether controlled cord traction can be omitted from active management of this stage without increasing the risk of severe haemorrhage.

Methods We did a multicentre, non-inferiority, randomised controlled trial in 16 hospitals and two primary health-care centres in Argentina, Egypt, India, Kenya, the Philippines, South Africa, Thailand, and Uganda. Women expecting to deliver singleton babies vaginally (ie, not planned caesarean section) were randomly assigned (in a 1:1 ratio) with a centrally generated allocation sequence, stratified by country, to placental delivery with gravity and maternal effort (simplified package) or controlled cord traction applied immediately after uterine contraction and cord clamping (full package). After randomisation, allocation could not be concealed from investigators, participants, or assessors. Oxytocin 10 IU was administered immediately after birth with cord clamping after 1–3 min. Uterine massage was done after placental delivery according to local policy. The primary (non-inferiority) outcome was blood loss of 1000 mL or more (severe haemorrhage). The non-inferiority margin for the risk ratio was 1·3. Analysis was by modified intention-to-treat, excluding women who had emergency caesarean sections. This trial is registered with the Australian and New Zealand Clinical Trials Registry, ACTRN 12608000434392.

Findings Between June 1, 2009, and Oct 30, 2010, 12227 women were randomly assigned to the simplified package group and 12163 to the full package group. After exclusion of women who had emergency caesarean sections, 11861 were in the simplified package group and 11820 were in the full package group. The primary outcome of blood loss of 1000 mL or more had a risk ratio of 1·09 (95% CI 0·91–1·31) and the upper 95% CI limit crossed the pre-stated non-inferiority margin. One case of uterine inversion occurred in the full package group. Other adverse events were haemorrhage-related.

Interpretation Although the hypothesis of non-inferiority was not met, omission of controlled cord traction has very little effect on the risk of severe haemorrhage. Scaling up of haemorrhage prevention programmes for non-hospital settings can safely focus on use of oxytocin.

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See Comment page 1684

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Introduction

Post-partum haemorrhage is a major cause of severe morbidity and maternal death, particularly in Africa and Asia, where nearly a third of pregnancy-related deaths are associated with haemorrhage.[1] Most such deaths occur because of insufficient uterine contraction soon after birth. Two management packages for the third stage of labour are commonly used, known as active management and expectant management.[2] In active management, several prophylactic interventions are applied in combination. WHO recommends administration of oxytocin soon after delivery of the baby, controlled cord traction, and delayed clamping and cutting of the cord until the health-care worker is ready to apply traction.[3] Uterine massage after placental delivery is included in professional society guidelines.[4] In expectant management, the interventions included in active management are withheld unless needed. Randomised trials[5,6] of active versus expectant management have been done in hospital settings and they included early clamping and cutting of the cord in addition to the WHO components. Overall, the risk of post-partum haemorrhage was more than 60% lower with active management than with expectant management. The timing of cord clamping does not seem to play a significant part in blood loss.[7] Side-effects such as increased blood pressure, nausea, vomiting, and increased placental retention are generally attributed to the use of uterotonic ergot alkaloids.

WHO recommendations published in 2007[3] advocated use of the full active management package, while


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Research Focus: Calcium and Pre-eclampsia

Calcium and Pre-eclampsia

Hypertensive disorders of pregnancy are extremely prevalent in South Africa and a major cause of maternal and perinatal mortality and morbidity globally. Over the last 20 years, in collaboration with colleagues around the world, the ECRU team has made a significant contribution to addressing important knowledge gaps in this field, through both primary research and evidence synthesis.

Primary research

The WHO Calcium Supplementation for the Prevention of Pre-eclampsia Trial (2001–2006)

This landmark trial coordinated by the WHO, involving 8,325 nulliparous women from populations with low dietary calcium intake, was a multicenter collaboration between research centers in Argentina, Egypt, India, Peru, South Africa, and Vietnam. One of the first international collaborations embarked upon by ECRU at its East London site, ECRU contributed numerous participants over the 6-year course of the study.

Findings from this trial showed significant reductions in eclampsia, severe gestational hypertension and other severe morbidity among women receiving calcium supplementation (1.5 g per day) from 20 weeks of pregnancy, but the reduction in pre-eclampsia was small and non-statistically significant.

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World Health Organization randomized trial of calcium supplementation among low calcium intake pregnant women

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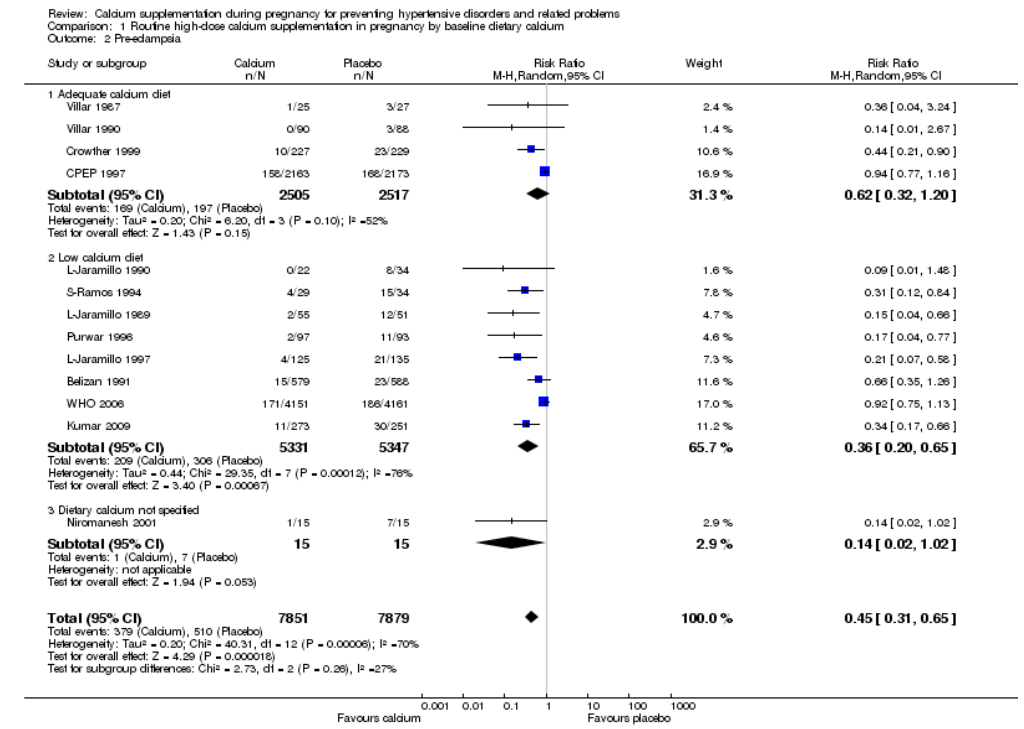
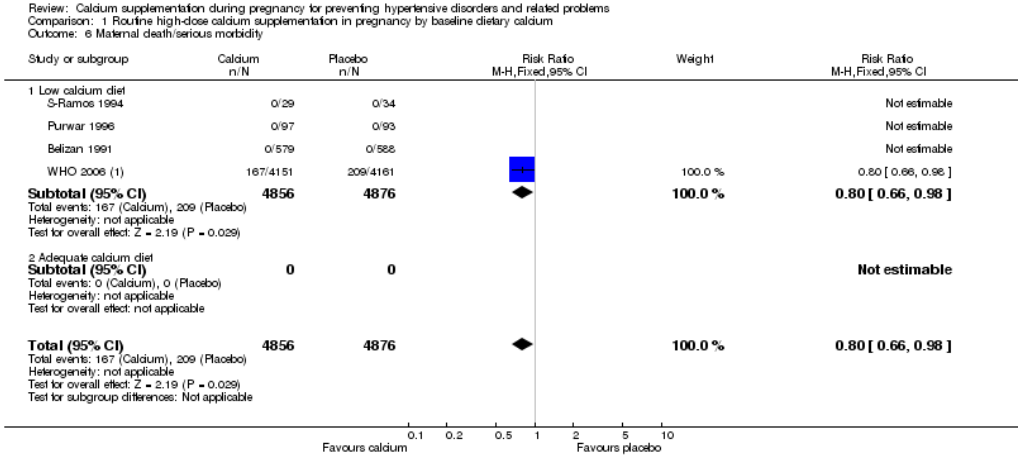
KEY WORDS
Preeclampsia
Calcium supplement
Preterm delivery

Objective: The purpose of this trial was to determine whether calcium supplementation of pregnant women with low calcium intake reduces preeclampsia and preterm delivery.
Study design: Randomized placebo-controlled, double-blinded trial in nulliparous normotensive women from populations with dietary calcium <600 mg/d. Women who were recruited before gestational week 20 received supplements (1.5 g calcium/d or placebo) throughout pregnancy.

Primary outcomes were preeclampsia and preterm delivery; secondary outcomes focused on severe morbidity and maternal and neonatal mortality rates.
Results: The groups comprised 8325 women who were assigned randomly. Both groups had similar gestational ages, demographic characteristics, and blood pressure levels at entry. Compliance were both 85% and follow-up losses (calcium, 3.4%; placebo, 3.7%). Calcium supplementation was associated with a non-statistically significant small reduction in preeclampsia (4.1% vs 4.5%) that was evident by 35 weeks of gestation (1.2% vs 2.8%; $P = .04$). Eclampsia (risk ratio, 0.68: 95% CI, 0.48-0.97) and severe gestational hypertension (risk ratio, 0.71; 95% CI, 0.61-0.82) were significantly lower in the calcium group. Overall, there was a reduction in the severe preeclamptic complications index (risk ratio, 0.76; 95% CI, 0.66-0.89; life-table analysis, log rank test; $P = .04$). The severe maternal morbidity and mortality index was also reduced in the supplementation group (risk ratio, 0.80; 95% CI, 0.70-0.91). Preterm delivery (the neonatal primary outcome) and early preterm delivery tended to be reduced among women who were ≤20 years of age (risk ratio, 0.82; 95% CI, 0.67-1.01; risk ratio, 0.64; 95% CI, 0.42-0.98, respectively). The neonatal mortality rate was lower (risk ratio, 0.70; 95% CI, 0.56-0.88) in the calcium group.
Conclusion: A 1.5-g calcium/day supplement did not prevent preeclampsia but did reduce its severity, maternal morbidity, and neonatal mortality, albeit these were secondary outcomes.





(1) WHO Severe maternal morbidity and mortality index. Defined as "At least 1 of the following: Admission to intensive care or any special care unit, eclampsia, severe preeclampsia, placental al

Research Focus: Calcium and Pre-eclampsia

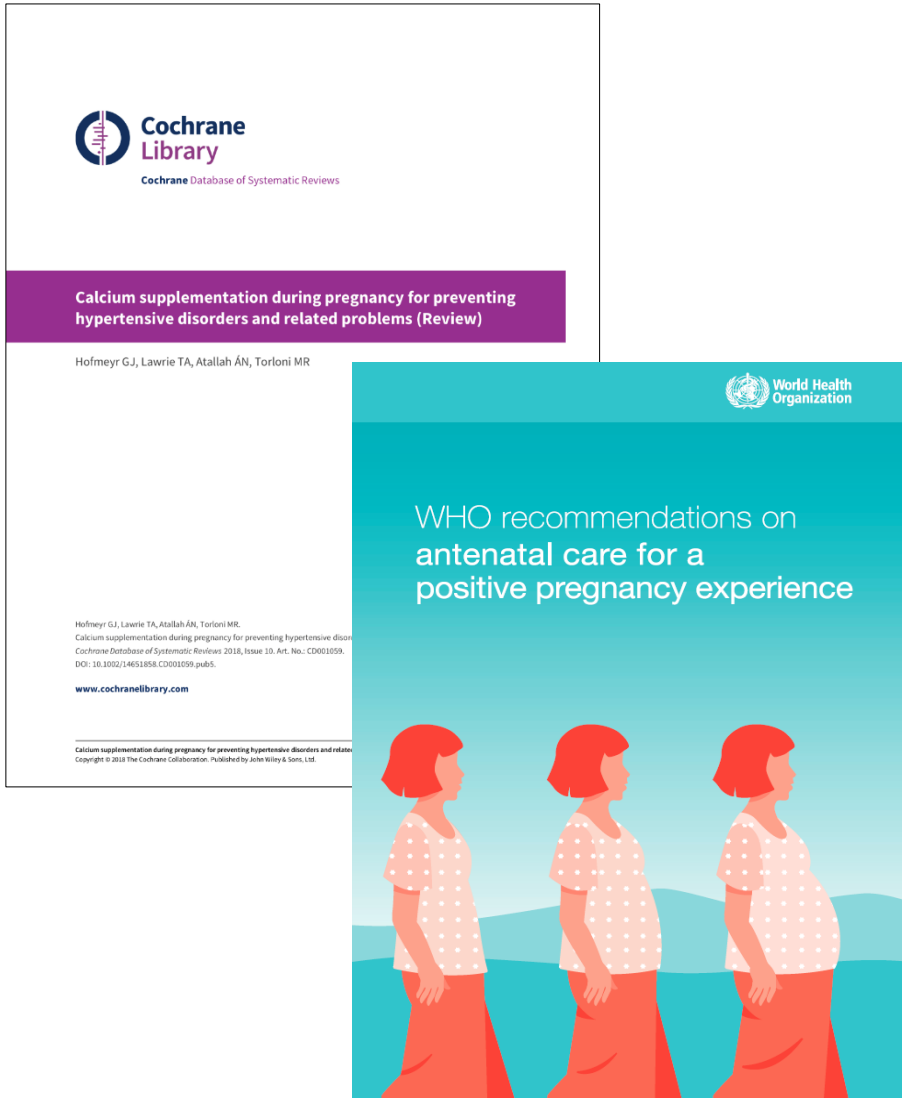
Evidence synthesis

In 2000, the ECRU Director led a Cochrane systematic review to evaluate the effect of calcium supplementation on hypertensive disorders of pregnancy. This review, which includes data from the 2006 WHO calcium trial, has since undergone four updates, most recently in 2018. A key finding from the review, which includes 27 studies in total, was that calcium supplementation might reduce the risk of pre-eclampsia on average by 55% (95% confidence interval, 35% to 69%).

In addition, subgroup findings suggested that this benefit would be greater among women with low dietary calcium intake and those at high risk of pre-eclampsia than among women without risk factors and with adequate diets. Another important finding was that calcium could reduce maternal death or serious morbidity in pregnancy by about 20%.

The extent of these effects of calcium supplementation on pre-eclampsia and its associated morbidity remains uncertain, however, due to small studies effects observed by the reviewers. The findings were interpreted to mean that, in settings where dietary calcium is low, calcium supplementation could be an important strategy to reduce the serious consequences of pre-eclampsia.

Research Focus: Calcium and Pre-eclampsia



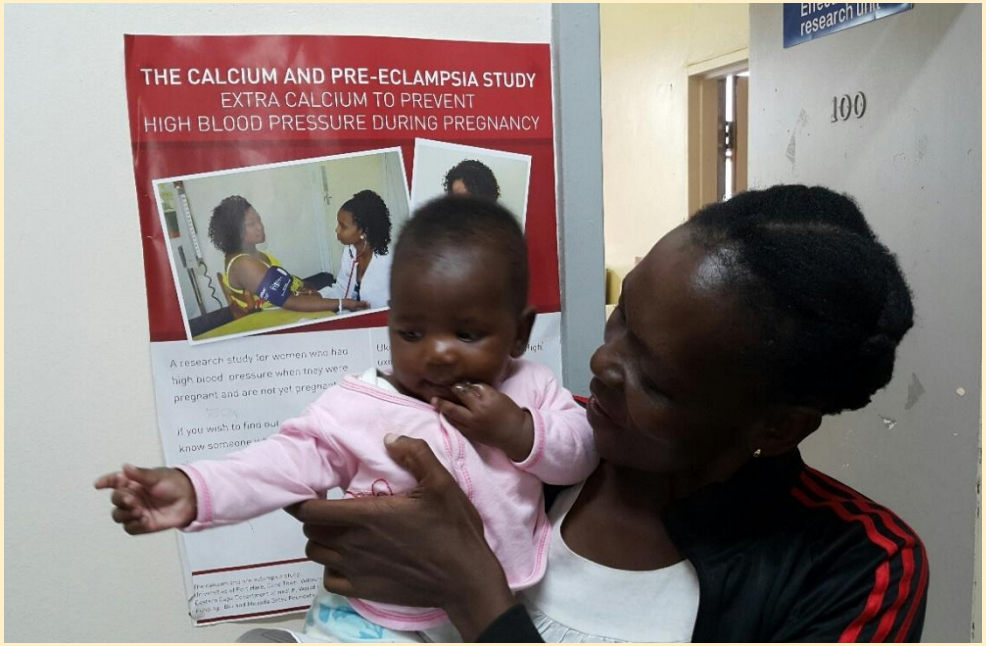
Research impact

ECRU's collaborative work on calcium supplementation in pregnancy has made a significant contribution to the evidence base on calcium supplementation in pregnancy and has led to changes in clinical practice, for example, by informing international clinical guidelines, such as the 2016 World Health Organization antenatal care guideline.

WHO recommendation:

"In populations with low dietary calcium intake, daily calcium supplementation (1.5–2.0 g oral elemental calcium) is recommended for pregnant women to reduce their risk of pre-eclampsia."

Source: WHO recommendations on antenatal care for a positive pregnancy experience (2016)



Research Focus: Calcium and Pre-eclampsia

Research Focus: Calcium and Pre-eclampsia

Primary research

Pre-pregnancy and early pregnancy calcium supplementation: The Calcium And Pre-eclampsia (CAP) trial (2010–2018)

This WHO-coordinated collaborative trial was commenced in 2010, to determine whether calcium supplementation started before pregnancy, and continued throughout pregnancy, improved pregnancy outcomes among women who had experienced pre-eclampsia in a previous pregnancy. The trial was funded by the University of British Columbia, a grantee of the Bill & Melinda Gates Foundation, as part of the PRE-EMPT research program.

The three participating countries in this trial, conducted in populations with low dietary calcium intake, were Argentina, South Africa and Zimbabwe. ECRU coordinated recruitment at the South African study sites, which included East London Hospital Complex, Chris Hani Baragwanath Hospital (Johannesburg), Mowbray Maternity Hospital (university of Cape Town), and Tygerberg Hospital (Parow).

Findings showed a reduction in recurrent pre-eclampsia among pregnant women receiving calcium supplementation from the pre-conception period (23% vs 29%); however, the reduction was of borderline significance.

Trials of interventions commenced before pregnancy to improve pregnancy outcomes are rare because they are challenging to conduct. Participants (non-pregnant and pregnant) require rigorous follow up over a long period. Recruitment of the 1,354 women randomized in this trial took five years. Notably, of these, 70.5% were from South African sites – testimony to ECRU's capacity to recruit and retain participants, even in lengthy pre-conception trials.

CAP Steering Committee
Back row: Alvaro Ciganda, Jim Roberts, Ana Pilar Bétran, Justus Hofmeyr
Middle Row: Simpiwe Mose, Armando Seuc, Gabriela Cormick, Susan Fawcus
Front row: Mandisa Singata-Madliki, Stephen Munjanja, Eduardo Bergel

Prepregnancy and early pregnancy calcium supplementation among women at high risk of pre-eclampsia: a multicentre, double-blind, randomised, placebo-controlled trial

G Justus Hofmeyr, Ana Pilar Betrán, Mandisa Singata-Madliki, Gabriela Cormick, Stephen P Munjanja, Susan Fawcus, Simpiwe Mose, David Hall, Alvaro Ciganda, Armando H Seuc, Theresa A Lawrie, Eduardo Bergel, James M Roberts, Peter von Dadelszen, José M Belizán, and the Calcium and Pre-eclampsia Study Group*

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See Comment page 298

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Summary

Background Reducing deaths from hypertensive disorders of pregnancy is a global priority. Low dietary calcium might account for the high prevalence of pre-eclampsia and eclampsia in low-income countries. Calcium supplementation in the second half of pregnancy is known to reduce the serious consequences of pre-eclampsia; however, the effect of calcium supplementation during placentation is not known. We aimed to test the hypothesis that calcium supplementation before and in early pregnancy (up to 20 weeks' gestation) prevents the development of pre-eclampsia

Methods We did a multicountry, parallel arm, double-blind, randomised, placebo-controlled trial in South Africa, Zimbabwe, and Argentina. Participants with previous pre-eclampsia and eclampsia received 500 mg calcium or placebo daily from enrolment prepregnancy until 20 weeks' gestation. Participants were parous women whose most recent pregnancy had been complicated by pre-eclampsia or eclampsia and who were intending to become pregnant. All participants received unblinded calcium 1·5 g daily after 20 weeks' gestation. The allocation sequence (1:1 ratio) used computer-generated random numbers in balanced blocks of variable size. The primary outcome was pre-eclampsia, defined as gestational hypertension and proteinuria. The trial is registered with the Pan-African Clinical Trials Registry, number PACTR201105000267371. The trial closed on Oct 31, 2017.

Findings Between July 12, 2011, and Sept 8, 2016, we randomly allocated 1355 women to receive calcium or placebo; 331 of 678 participants in the calcium group versus 320 of 677 in the placebo group became pregnant, and 298 of 678 versus 283 of 677 had pregnancies beyond 20 weeks' gestation. Pre-eclampsia occurred in 69 (23%) of 296 participants in the calcium group versus 82 (29%) of 283 participants in the placebo group with pregnancies beyond 20 weeks' gestation (risk ratio [RR] 0·80, 95% CI 0·61–1·06; p=0·121). For participants with compliance of more than 80% from the last visit before pregnancy to 20 weeks' gestation, the pre-eclampsia risk was 30 (21%) of 144 versus 47 (32%) of 149 (RR 0·66, CI 0·44–0·98; p=0·037). There were no serious adverse effects of calcium reported.

Interpretation Calcium supplementation that commenced before pregnancy until 20 weeks' gestation, compared with placebo, did not show a significant reduction in recurrent pre-eclampsia. As the trial was powered to detect a large effect size, we cannot rule out a small to moderate effect of this intervention.

Funding The University of British Columbia, a grantee of the Bill & Melinda Gates Foundation; UNDP–UNFPA–UNICEF–WHO–World Bank Special Programme of Research, Development and Research Training in Human Reproduction, WHO; the Argentina Fund for Horizontal Cooperation of the Argentinean Ministry of Foreign Affairs; and the Centre for Intervention Science in Maternal and Child Health.

Introduction

Hypertension is estimated to complicate 5% of all pregnancies and 11% of first pregnancies, and half of these cases are associated with pre-eclampsia (gestational hypertension plus proteinuria).[1] Hypertensive disorders of pregnancy are the direct cause of death of about 30 000 women annually,[2] or approximately 14% of maternal deaths,[3] most of which occur in low-income countries. In a survey of 29 countries in Africa, Asia, Latin America, and the Middle East, 25·9% of women with severe maternal outcomes (ie, maternal death or near miss death) had pre-eclampsia or eclampsia, which was the direct cause of 20% of reported maternal deaths in these country settings.[4] Therefore, reducing maternal mortality and

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journal homepage: www.elsevier.com/locate/preghy

Original Article

The effect of calcium supplementation on blood pressure in non-pregnant women with previous pre-eclampsia: An exploratory, randomized placebo controlled study

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ABSTRACT

Background: Epidemiological findings suggest that the link between poverty and pre-eclampsia might be dietary calcium deficiency. Calcium supplementation has been associated with a modest reduction in pre-eclampsia, and also in blood pressure (BP).
Methods: This exploratory sub-study of the WHO Calcium and Pre-eclampsia (CAP) trial aims to determine the effect of 500 mg/day elemental calcium on the blood pressure of non-pregnant women with previous pre-eclampsia. Non-pregnant women with at least one subsequent follow-up trial visit at approximately 12 or 24 weeks after randomization were included.
Results: Of 836 women randomized by 9 September 2014, 1st visit data were available in 367 women of whom 217 had previously had severe pre-eclampsia, 2nd visit data were available in 201 women. There was an overall trend to reduced BP in the calcium supplementation group (1–2.5 mmHg) although differences were small and not statistically

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Research Focus: Calcium and Pre-eclampsia

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Trials

RESEARCH Open Access

Participant recruitment and retention in longitudinal preconception randomized trials: lessons learnt from the Calcium And Pre-eclampsia (CAP) trial

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Abstract

Background: The preconception period has the potential to influence pregnancy outcomes and randomized controlled trials (RCTs) are needed to evaluate a variety of potentially beneficial preconception interventions. However, RCTs commencing before pregnancy have significant participant recruitment and retention challenges. The Calcium And Pre-eclampsia trial (CAP trial) is a World Health Organization multi-country RCT of calcium supplementation commenced before pregnancy to prevent recurrent pre-eclampsia in which non-pregnant participants are recruited and followed up until childbirth. This sub-study explores recruitment methods and preconception retention of participants of the CAP trial to inform future trials.

Methods: Recruiters at the study sites in Argentina, South Africa and Zimbabwe completed post-recruitment phase questionnaires on recruitment methods used. Qualitative data from these questionnaires and quantitative data on pre-pregnancy trial visit attendance and pregnancy rates up to September 2016 are reported in this paper. RStudio (Version 0.99.903 https://www.rstudio.org) statistical software was used for summary statistics.

Results: Between July 2011 and 8 September 2016, 1354 women with previous pre-eclampsia were recruited. Recruitment took 2 years longer than expected and was facilitated mainly through medical record/register and maternity ward/clinic-based strategies. Recruiters highlighted difficulties associated with inadequate medical records, redundant patient contact details, and follow-up of temporarily ineligible women as some of the challenges faced. Whilst the attendance rates at pre-pregnancy visits were high (78% or more), visits often occurred later than scheduled. Forty-five percent of participants became pregnant (614/1354), 33.5% (454/1354) within 1 year of randomization.

(Continued on next page)

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BMC Pregnancy and Childbirth

RESEARCH ARTICLE Open Access

Are women with history of pre-eclampsia starting a new pregnancy in good nutritional status in South Africa and Zimbabwe?

Gabriela Cormick[1,2*], Ana Pilar Betrán[3], Janetta Harbron[2], Tina Dannemann Purnat[4], Catherine Parker[5,6,7], David Hall[8], Armando H. Seuc[9], James M. Roberts[10], José M. Belizán[1], G. Justus Hofmeyr[5,6,7] and on behalf of the Calcium and Pre-eclampsia Study Group

Abstract

Background: Maternal nutritional status before and during pregnancy is an important contributor to pregnancy outcomes and early child health. The aim of this study was to describe the preconceptional nutritional status and dietary intake during pregnancy in high-risk women from South Africa and Zimbabwe.

Methods: This is a prospective observational study, nested to the CAP trial. Anthropometric measurements before and during pregnancy and dietary intake using 24-h recall during pregnancy were assessed. The Intake Distribution Estimation software (PC-SIDE) was used to evaluate nutrient intake adequacy taking the Estimated Average Requirement (EAR) as a cut-off point.

Results: Three hundred twelve women who had pre-eclampsia in their last pregnancy and delivered in hospitals from South Africa and Zimbabwe were assessed. 73.7 and 60.2% women in South Africa and Zimbabwe, respectively started their pregnancy with BMI above normal (BMI ≥ 25) whereas the prevalence of underweight was virtually non-existent. The majority of women had inadequate intakes of micronutrients. Considering food and beverage intake only, none of the micronutrients measured achieved the estimated average requirement. Around 60% of pregnant women reported taking folic acid or iron supplements in South Africa, but almost none did so in Zimbabwe.

Conclusion: We found a high prevalence of overweight and obesity and high micronutrient intake inadequacy in pregnant women who had the previous pregnancy complicated with pre-eclampsia. The obesity figures and micronutrient inadequacy are issues of concern that need to be addressed. Pregnant women have regular contacts with the health system; these opportunities could be used to improve diet and nutrition.

Trial registration: PACTR201105000267371. Registered 06 December 2010.

Keywords: Nutrient intake, Weight, Pregnancy, Supplement, Obesity, BMI

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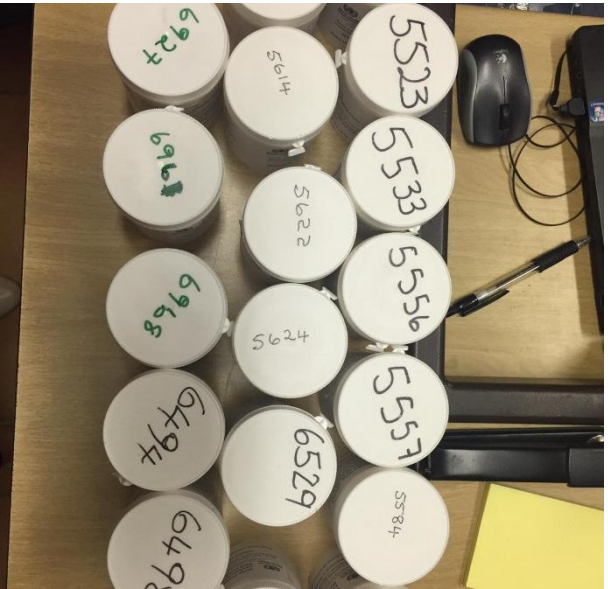
Welcome To
HARARE CENTRAL
MATERNITY HOSPITAL


Research Focus: Calcium and Pre-eclampsia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HARARE MATERNITY
HOSPITAL

Onsite Midwife-led Birth Units

To embrace and enhance the normality of childbirth, many countries have introduced midwifery units to provide holistic and midwife-led care, which is associated with the increased likelihood of a spontaneous vaginal birth, fewer obstetric interventions, and a leaning towards increased maternal satisfaction.

South Africa's health system is based on the primary care model in which 'low-risk' maternity care is provided at clinics and community health-care centres, and 'high-risk' maternity care is provided at hospitals. In South Africa, the most distinct separation of primary from secondary/tertiary services is usually geographic.

As a result, there are potentially critical delays in managing unexpected complications arising in otherwise low-risk pregnancies. In addition, there are some 'low-risk' women who receive birth care in secondary hospitals, thereby using expensive resources, often with unnecessary obstetric interventions.

Recognising the need to re-evaluate the maternity care model in South Africa, ECRU has made a significant local and international

contribution towards maternity care through its development of the Onsite Midwife-led Birth Unit concept. The OMBU model of care, adapted to the South African health system, allows women considered to be at low risk of pregnancy complications to choose between giving birth in a community health centre or in an OMBU.

In the South African context, the OMBU is staffed, administered and funded by the primary care service, but is located within a hospital and is midwife-led until the point of up-referral. This ensures comprehensive emergency obstetric and newborn care, whilst ensuring a normal birth experience for women without complications.

Primary research

The OMBU at Frere Hospital opened in March 2012. To evaluate the impact of the OMBU on Frere's maternity services, ECRU audited routinely collected data from the two 12 month periods before and after the OMBU opened, and published the findings in *BMC Pregnancy and Childbirth* in 2014. Data on the number of births, maternal and perinatal deaths, and mode of birth were among the retrospectively retrieved data and are shown in the table below.

Outcome	Before	After opening of OMBU		
	Frere	Frere	OMBU	Frere + OMBU
Mothers giving birth	6352	5764	1611	7375
Babies born	6470 (100%)	5875 (89%)	1613 (25%)	7488 (114%)
Perinatal deaths	268	250	2	252
Perinatal mortality/1000	41.4	42.6	1.2	33.6
Maternal deaths	14	6	0	6
Maternal deaths/100000	220	104	0	81
Caesarean sections	2412	2574	0	2574
Caesarean sections (%)	38%	45%		35%

Table of audit findings for the 12 months before and after the OMBU opened

Findings of the audit showed a 14% increase in the number of births at the combined facility, with 11% fewer births occurring within Frere Hospital itself. There was also a 10% reduction in caesarean sections at Frere Hospital in the post-OMBU cohort and perinatal and maternal mortality data compared favourably with the pre-OMBU period. Authors cautioned against over-interpreting the findings, however, as observational studies such as these are at risk of bias and many factors could have influenced these outcomes.

Evidence synthesis

The 2014 ECRU paper was included in a systematic review of OMBUs published in *BMJ Global Health* in 2016, of which Justus Hofmeyr was a co-author. Of the ten included randomized and observational studies, one was from a low-income country, three were from middle-income countries, and six were from high-income countries.

The systematic review findings suggested that OMBUs could be a feasible, cost-effective and desirable alternative to standard models of maternity care, particularly in settings where timely referral to emergency care is challenging.

Research Focus: Onsite Midwife-led Birth Units

Principle benefits of the OMBU model

- *Low-risk pregnant women who present at the hospital in labour can be triaged directly to the OMBU, rather than being sent or receiving inappropriate secondary level care in the hospital obstetric unit (OU).*
- *Greater capacity for more low-risk women to give birth on the hospital premises, thereby increasing access to emergency care.*
- *Timely management of complications by transfer or consultation.*
- *Highly motivated staff due to ongoing professional development, supervision and dedicated nature of the unit.*
- *Increased quality of care due to focus on philosophy of midwifery care.*
- *Increased capacity for complicated pregnancies in a less crowded hospital OU.*
- *Improved birth experience for women, leading to an improved reputation of the institution, which will encourage service uptake.*

Research impact

OMBUs could be considered for any secondary or tertiary care hospital in South Africa, and possibly for other countries with similar primary care health system models; however, their potential to improve uptake maternity services, save money, and improve birth outcomes needs corroboration.

ECRU plans to conduct further research to evaluate the advantages of the OMBU model and refine the model to further enhance the midwifery philosophy of pregnancy and childbirth. Ultimately, a large, cluster-randomized trial will be necessary to evaluate whether the observed reductions in maternal and perinatal deaths, as suggested by the Frere OMBU audit, represent real risk reductions.

Research Focus: Onsite Midwife-led Birth Units

Hofmeyr et al. BMC Pregnancy and Childbirth (2014) 14:417
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BMC Pregnancy & Childbirth

RESEARCH ARTICLE Open Access

Audit of a new model of birth care for women with low risk pregnancies in South Africa: the primary care onsite midwife-led birth unit (OMBU)

George Justus Hofmeyr[1,2,3*], Thozeka Mancotywa[3], Nomvula Silwana-Kwadjo[3], Batembu Mgudlwa[2,3], Theresa A Lawrie[4] and Ahmet Metin Gülmezoglu[4]

Abstract

Background: South Africa's health system is based on the primary care model in which low-risk maternity care is provided at community health centres and clinics, and 'high-risk' care is provided at secondary/tertiary hospitals. This model has the disadvantage of delays in the management of unexpected intrapartum complications in otherwise low-risk pregnancies, therefore, there is a need to re-evaluate the models of birth care in South Africa. To date, two primary care onsite midwife-led birth units (OMBUs) have been established in the Eastern Cape. OMBUs are similar to alongside midwifery units but have been adapted to the South African health system in that they are staffed, administered and funded by the primary care service. They allow women considered to be at 'low risk' to choose between birth in a community health centre and birth in the OMBU.

Methods: The purpose of this audit was to evaluate the impact of establishing an OMBU at Frere Maternity Hospital in East London, South Africa, on maternity services. We conducted an audit of routinely collected data from Frere Maternity Hospital over two 12 month periods, before and after the OMBU opened. Retrospectively retrieved data included the number of births, maternal and perinatal deaths, and mode of delivery.

Results: After the OMBU opened at Frere Maternity Hospital, the total number of births on the hospital premises increased by 16%. The total number of births in the hospital obstetric unit (OU) dropped by 9.3%, with 1611 births out of 7375 (22%) occurring in the new OMBU. The number of maternal and perinatal deaths was lower in the post-OMBU period compared with the pre-OMBU period. These improvements cannot be assumed to be the result of the intervention as observational studies are prone to bias.

Conclusions: The mortality data should be interpreted with caution as other factors such as change in risk profile may have contributed to the death reductions. There are many additional advantages for women, hospital staff and primary care staff with this model, which may also be more cost-effective than the standard (freestanding) primary care model.

Keywords: Midwife-led unit, Primary birth care, Onsite birth unit, OMBU

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BMJ Global Health

Onsite midwife-led birth units (OMBUs) for care around the time of childbirth: a systematic review

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► Additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjgh-2016-000096).

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ABSTRACT

Introduction: To ensure timely access to comprehensive emergency obstetric care in low- and middle-income countries, a number of interventions have been employed. This systematic review assesses the effects of onsite midwife-led birth units (OMBUs) embedded within hospitals which provide comprehensive emergency obstetric and newborn care.

Methods: Both interventional and observational studies that compared OMBUs with standard medical-led obstetric care were eligible for inclusion. Cochrane Central Register of Controlled Trials, PubMed/Medline, EMBASE, CINAHL, Science Citation and Social Sciences Citation Index, Global Health Library and one Chinese database were searched. Meta-analysis was conducted to synthesise data from randomised controlled trials (RCTs). Findings of observational studies were summarised by forest plots with brief narratives.

Results: Three RCTs, one controlled before-and-after study and six cohort studies were included. There were no or very few maternal and perinatal deaths in either OMBUs or standard obstetric units, with no significant differences between the two. Women giving birth in OMBUs were less likely to use epidural analgesia (risk ratio (RR) 0.67, 95% CI 0.55 to 0.82; three trials, n=2431). The UK national cohort study and two other cohorts in China and Nepal found less oxytocin augmentation, more spontaneous vaginal deliveries, fewer caesarean sections and fewer episiotomies performed in OMBUs than in standard obstetric units. These differences were not statistically significant in RCTs and the remaining cohorts. One study investigated satisfaction with midwife-led birth care among women and midwives, with positive findings in both groups favouring OMBUs. In addition, two studies found that the total cost of birth was lower in OMBUs than in standard obstetric units.

Conclusions: OMBUs could be an alternative model for providing safe and cost-effective childbirth care, which may be particularly important in low- and middle-income countries to meet the growing demand for facility-based birth for low-risk women and improve efficiency of health systems.

Key questions

What is already known about this topic?

- Globally, facility-based childbirth has been identified as a key strategy to improve the safety of intrapartum care, particularly in low- and middle-income countries. Although progress has been made in many low- and middle-income countries, poorly staffed and equipped primary health facilities and non-functional referral systems have been recognised as constraints to improving maternal and newborn health outcomes.
- In response to potential efficiency and safety concerns of stand-alone low-risk units, onsite midwife-led birth units (OMBUs) that are adjacent to higher level care obstetric units have been introduced in some countries.

What are the new findings?

- This systematic review synthesised available evidence from interventional and observational studies and concluded that OMBUs could be an alternative model for providing safe and cost-effective childbirth care, which may provide important benefits, particularly in settings where referral systems do not function well and access to care in a timely fashion is challenging.

Recommendations for policy

- Being adjacent to the obstetric unit for managing complications occurring in the intrapartum period is particularly important in many low- and middle-income countries where large numbers of maternal and neonatal deaths occur in health facilities because of failure to detect complications or lack of timely transfer of a woman to a facility with comprehensive emergency care.
- In the introduction of OMBUs, targeted pro-poor interventions should be developed to ensure equality in accessing such care.

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BACKGROUND

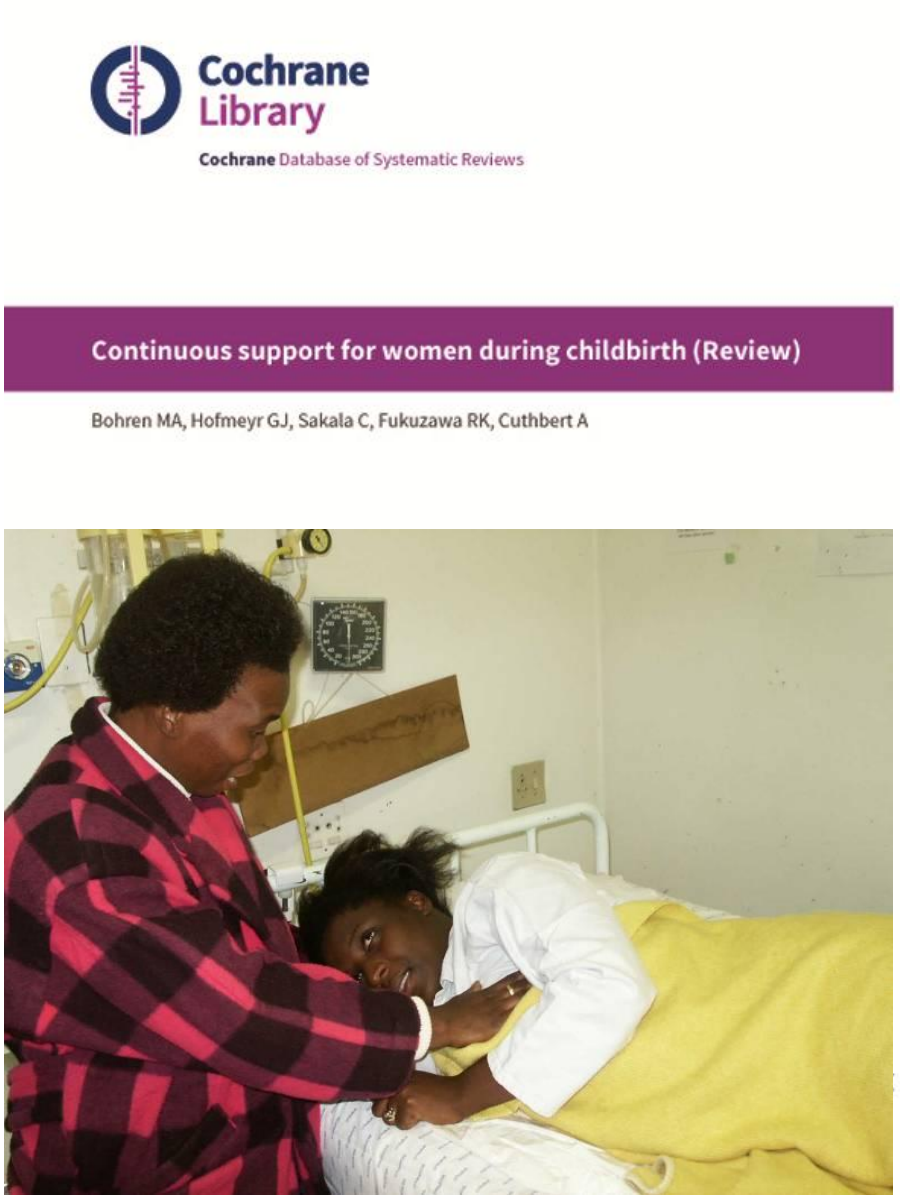
Globally, facility-based childbirth has been identified as a key strategy to improve the safety of intrapartum care, particularly in low- and middle-income countries.[1] This is critical, given that over two-thirds of maternal deaths and nearly one-third of stillbirths and neonatal deaths globally occur around the

Companionship in labour

On-site Midwife-led Birth Units (OMBUs) facilitate the provision of low-intervention, respectful maternity care. The component of respectful maternity care for which there is the most robust evidence of benefit is that of labour companionship.

Labour companionship includes emotional support from the continuous presence of another person, reassurance and praise, information about labour progress and coping techniques, comfort measures such as massage and warm baths, promoting adequate fluid intake and output, and having someone to speak up on behalf of their behalf, when needed.

Working in collaboration with local and international colleagues, ECRU has led research in this field, contributing substantial evidence on the major positive effects of this vital yet frequently unobserved supportive practice.



BMC Medicine

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Research article

Open Access

Promoting childbirth companions in South Africa: a randomised pilot study

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Abstract

Background: Most women delivering in South African State Maternity Hospitals do not have a childbirth companion; in addition, the quality of care could be better, and at times women are treated inhumanely. We piloted a multi-faceted intervention to encourage uptake of childbirth companions in state hospitals, and hypothesised that lay carers would improve the behaviour of health professionals.

Methods: We conducted a pilot randomised controlled trial of an intervention to promote childbirth companions in hospital deliveries. We promoted evidence-based information for maternity staff at 10 hospitals through access to the World Health Organization Reproductive Health Library (RHL), computer hardware and training to all ten hospitals. We surveyed 200 women at each site, measuring companionship, and indicators of good obstetric practice and humanity of care. Five hospitals were then randomly allocated to receive an educational intervention to promote childbirth companions, and we surveyed all hospitals again at eight months through a repeat survey of postnatal women. Changes in median values between intervention and control hospitals were examined.

Results: At baseline, the majority of hospitals did not allow a companion, or access to food or fluids. A third of women were given an episiotomy. Some women were shouted at (17.7%, N = 2085), and a few reported being slapped or struck (4.3%, N = 2080). Despite an initial positive response from staff to the childbirth companion intervention, we detected no difference between intervention and control hospitals in relation to whether a companion was allowed by nursing staff, good obstetric practice or humanity of care.

Conclusion: The quality and humanity of care in these state hospitals needs to improve. Introducing childbirth companions was more difficult than we anticipated, particularly in under-resourced health care systems with frequent staff changes. We were unable to determine whether the presence of a lay carer impacted on the humanity of care provided by health professionals.

Trial registration: Current Controlled Trials ISRCTN33728802

Research Focus: Companionship in labour

Primary research

Before 2000, ECRU conducted primary research on the effects of labour companionship provided to women by community volunteers. This work showed that labour companionship could lead to a more positive labour experience, successful breastfeeding, less depression, and better self-esteem and confidence as a mother.

ECRU has subsequently built on this work by conducting a pilot cluster-randomized trial in 10 South African hospitals. The objective was to determine whether an educational package directed at maternity staff to increase the uptake of labour companions in hospitals would lead to more respectful maternity care by healthcare providers.

Findings showed that implementation of labour companionship is not straightforward and more work is needed to establish how to implement labour companionship in settings where it is not available *(Brown et al, 2007).*

Research Focus: Companionship in labour

Evidence synthesis

Members of the ECRU team co-authored a Cochrane systematic review entitled *"Continuous support for women during childbirth" (Bohren et al, 2017)*. The review included 26 trials with data from 17 countries, and involved more than 15,000 women in a wide range of settings and circumstances.

Review findings show that women receiving continuous support might have better pregnancy outcomes than those who do not, including a greater likelihood of having a spontaneous vaginal birth and a lessor likelihood of having a caesarean birth, instrumental vaginal birth, intrapartum analgesia and reporting negative feelings about their birth experience.

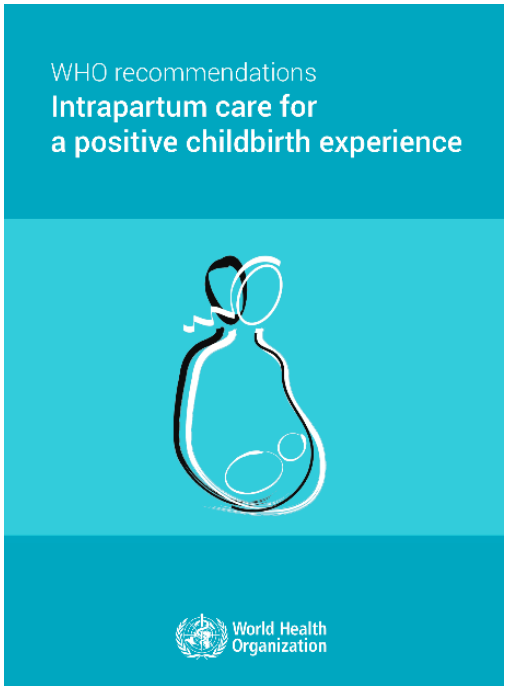
2018 WHO recommendations:

"A companion of choice is recommended for all women throughout labour and childbirth."

Source: WHO recommendations: intrapartum care for a positive childbirth experience (2018)

Research impact

The concepts of companionship during childbirth and respectful maternity care are now promoted globally in clinical practice guidelines.



2018 WHO recommendations:

"Respectful maternity care – which refers to care organized for and provided to all women in a manner that maintains their dignity, privacy and confidentiality, ensures freedom from harm and mistreatment, and enables informed choice and continuous support during labour and childbirth – is recommended."

Source: WHO recommendations: intrapartum care for a positive childbirth experience (2018)

Contraception

Expanding contraception options in South Africa

Using effective contraception enables women globally to avoid unwanted or high-risk pregnancies, and consequently numerous maternal and infant deaths are prevented. An estimated 65% of women in South Africa are currently using contraception; however, abortion and teenage pregnancy rates remain exceedingly high, in addition to high rates of HIV/AIDS and sexually transmitted diseases. HIV/AIDS has had a devastating impact on South African communities, as depicted in heart-wrenching tapestries by The Keiskamma Trust artists.

Evidence from observational studies suggest an increased risk of HIV acquisition among users of injectable depot medroxyprogesterone acetate (DMPA), which is the most commonly used contraceptive method in South Africa.

ECRU's research in this field aims to provide more reliable scientific data on the relative effects of different contraceptive methods, and to inform and expand contraceptive choice for women in South Africa and other low- and middle-income countries.

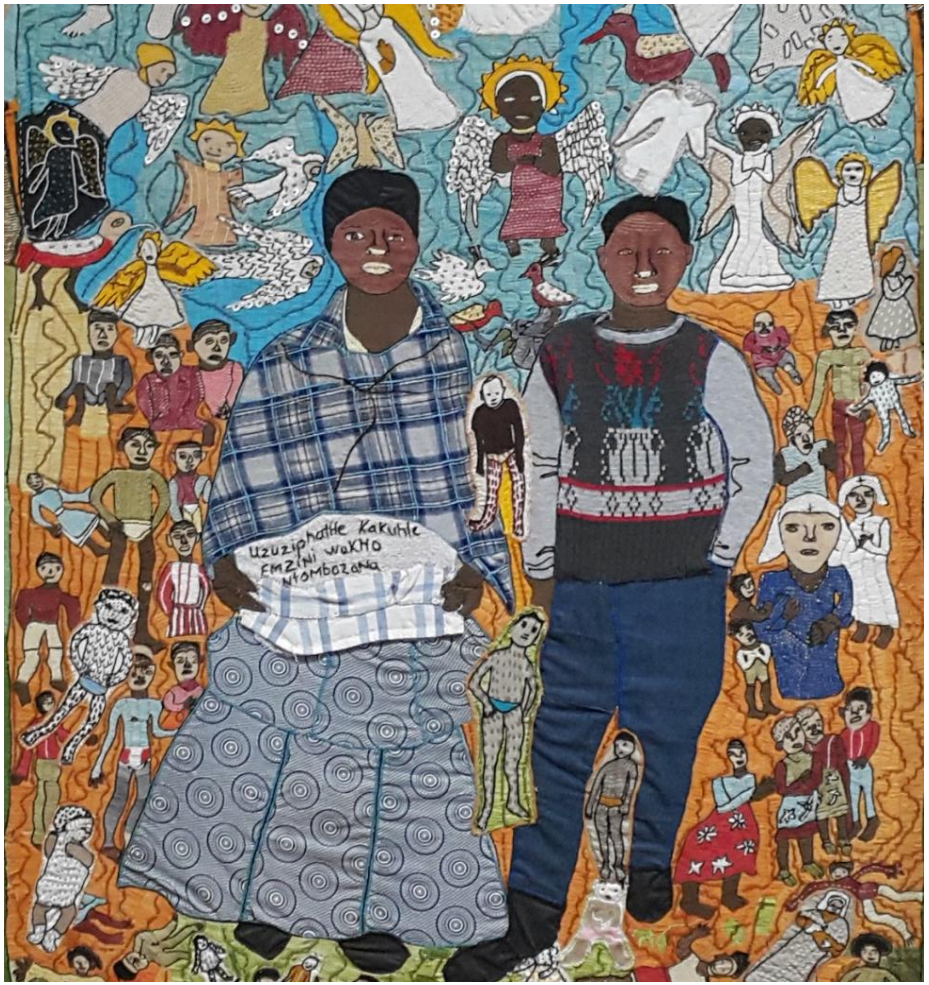
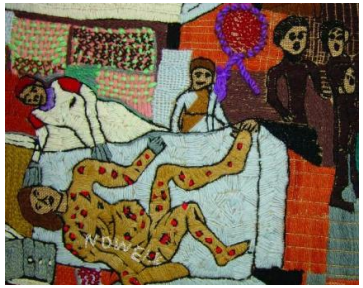


Photo: Courtesy of The Keiskamma Trust

Research Focus: Contraception



Primary research

Between July 2009 and November 2012, ECRU conducted the first large randomized controlled trial comparing commonly-used injectable progestogen contraceptives (IPC) with the copper intrauterine device (IUD), an under-utilized method in South Africa and other settings. Women requiring contraception after termination of pregnancy were recruited from Frere and Cecelia Makiwane Hospitals and pregnancy and discontinuation rates were measured, as well as HIV acquisition rates (a secondary outcome).

This pragmatic trial found that the IUD was more effective at preventing pregnancy than injectables (mainly DMPA) (5.8% pregnancy rate vs 8.4%, respectively), and found little difference in HIV acquisition rates (IUD vs IPC 3.5% vs 3.0% for intention-to-treat, and 3.4% vs 3.2% for per protocol analyses, respectively).

Table 2 Results for HIV acquisition according to intention-to-treat and per protocol analyses (initial method received)

	HIV acquisition		Effect estimate (IPC vs IUD)		
Analysis	***n* (%)**	***N***	**RR**	**95% CI**	***p***
ITT analysis (i.e. according to group allocation)					
IPC	20 (3.0)	656	0.88	0.48–1.59	0.7
IUD	22 (3.5)	634	1		

Source: Hofmeyr et al, BMC Reprod Health (2016)

Table 2 Pregnancy rates and outcomes

	IUD group (*N* = 971)		IPC group (*N* = 992)		RR	95 % CI	*P*-value (M-H)
	n	%	*n*	%			
Pregnancy (total)	56	5.8	83	8.4	0.69	0.50 to 0.96	0.025
Pregnancy outcome:							
Birth	29	3	41	4.1	0.72	0.45 to 1.15	0.17
Miscarriage	3	0.3	3	0.3			
Termination	2	0.2	2	0.2			
Ectopic	0	0	1	0.1			
Ongoing	16	1.6	29	2.9	0.56	0.31 to 1.03	0.059
Unknown	6	0.6	7	0.7			

IUD intrauterine device, *IPC* injectable progestin contraception, *RR* risk ratio, *CI* confidence interval, *M-H* mantel-haenszel chi square 2-tail

Table excerpt from Hofmeyr et al, J Fam Planning Reprod Health Care (2017)

However, due to its early closure, it was underpowered to detect a difference in the latter outcome. Whilst the target sample size of this original trial was 7,000, only 2,493 participants were accrued because the trial closed early, when the larger international multicentre trial described below was planned.

Ongoing primary research

The Evidence for Contraceptive Options and HIV Outcomes (ECHO) Study, is an open-label, randomized trial recruiting 7,800 women in four countries (Kenya, South Africa, Swaziland, Zambia). ECRU has played a pivotal role in the design and conduct of this rigorous trial, which aims to compare HIV acquisition and other outcomes of three highly-effective, reversible, long-acting contraceptive methods (LARCs), namely DMPA, a levonorgestrel (LNG) implant, and the copper IUD.

Top Left: Photo Courtesy of the Keiskamma Trust

Primary research

LARCs and postnatal depression

The provision of contraception in the immediate postnatal period is synonymous with the success of family planning programs in South Africa, and indeed worldwide. Although the World Health Organization does not recommend starting injectable progestogen contraception (IPC) before six weeks postpartum, the South African Department of Health does not restrict the use of injectable contraceptives in the postnatal period.

The effects of long-acting hormonal contraception on mood during the postnatal period, which is a time in a woman's life of huge hormonal and emotional changes, remain unclear.

To help to address this gap in knowledge, ECRU conducted a randomized controlled trial at Frere and Cecelia Makiwane Hospitals between 2012 and 2013 to determine whether DMPA increases the risk of postnatal depression compared with the IUD when administered after childbirth. In this study, which randomized 234 women within 48 hours of their giving birth, ECRU was unable to exclude an association between postnatal depression and DMPA.

ECRU concluded that postnatal women choosing to use DMPA should be counselled about the possibility of postnatal depression, until further evidence becomes available *(Singata-Madliki et al, 2016).*

Ongoing primary research

ECRU is currently conducting an ancillary to the ECHO study that it hopes will provide a more conclusive answer to the question of LARCs and depression. This ancillary study will compare rates of various undesirable outcomes, including depression and sexual dysfunction, between DMPA, the LNG implant, and the IUD, among 522 women enrolled in the larger ECHO trial *(Singata-Madliki et al, 2017).*

Recruitment and data collection for the ancillary study has now been completed and analysis of the study findings are underway. The ongoing ancillary study is funded by a grant from the South African Medical Research Council, which also funded the publication of the original 'IPC and postnatal depression' trial findings.

Research Focus: Contraception

Photo: Courtesy of The Keiskamma Trust

Gates Open Research

Gates Open Research 2018, 1:17 Last updated: 16 JUL 2018

STUDY PROTOCOL

REVISED Rationale and design of a multi-center, open-label, randomised clinical trial comparing HIV incidence and contraceptive benefits in women using three commonly-used contraceptive methods (the ECHO study) [version 2; referees: 2 approved]

G. Justus Hofmeyr[1*], Charles S. Morrison[2*], Jared M. Baeten[3], Tsungai Chipato[4], Deborah Donnell[5], Peter Gichangi[6-8], Nelly Mugo[9,10], Kavita Nanda[2], Helen Rees[11], Petrus Steyn[12], Douglas Taylor[2], ECHO Trial Team

v2 **First published:** 29 Dec 2017, **1**:17 (doi: 10.12688/gatesopenres.12775.1)
Latest published: 13 Mar 2018, **1**:17 (doi: 10.12688/gatesopenres.12775.2)

Abstract

Background: *In vitro*, animal, biological and observational clinical studies suggest that some hormonal methods, particularly depot medroxyprogesterone acetate – DMPA, may increase women's risk of HIV acquisition. DMPA is the most common contraceptive used in many countries worst affected by the HIV epidemic. To provide robust evidence for contraceptive decision-making among women, clinicians and planners, we are conducting the Evidence for Contraceptive Options and HIV Outcomes (ECHO) study in four countries with high HIV incidence and DMPA use: Kenya, South Africa, Swaziland, and Zambia (Clinical Trials.gov identifier NCT02550067).

Study design: We randomized HIV negative, sexually active women 16-35 years old requesting effective contraception and agreeing to participate to either DMPA, the copper T 380A intrauterine device or levonorgestrel implant. Participants attend a contraception support visit after 1 month and quarterly visits thereafter for up to 18 months. Participants receive a standard HIV prevention package and contraceptive side-effect management at each visit. The primary outcome is HIV seroconversion. Secondary outcomes include pregnancy, serious adverse events and method discontinuation. The sample size of 7800 women provides 80% power to detect a 50% relative increase in HIV risk between any of the three method pairs, assuming 250 incident infections per comparison.

Ethical considerations: Several WHO consultations have concluded that current evidence on HIV risk associated with DMPA is inconclusive and that a randomized trial is needed to guide policy, counselling and choice. Previous studies suggest that women without a specific contraceptive preference are willing to accept randomization to different contraceptive methods. Stringent performance standards are monitored by an independent data and safety monitoring board approximately every 6 months. The study has been conducted with extensive stakeholder engagement.

Conclusions: The ECHO study is designed to provide robust evidence on the relative risks (HIV acquisition) and benefits (pregnancy prevention) between three effective contraceptive methods.

Keywords

contraception, HIV acquisition, effectiveness, randomized trial, DMPA, IUD, implants

Hofmeyr et al. Reproductive Health (2016) 13:42
DOI 10.1186/s12978-016-0153-9

Reproductive Health

RESEARCH Open Access

Effects of the copper intrauterine device versus injectable progestin contraception on pregnancy rates and method discontinuation among women attending termination of pregnancy services in South Africa: a pragmatic randomized controlled trial

G. Justus Hofmeyr[1], Mandisa Singata-Madliki[1], Theresa A. Lawrie[1,5*], Eduardo Bergel[4] and Marleen Temmerman[2,3]

Abstract

Background: The copper intrauterine device (IUD) is under-utilised in South Africa, where injectable progestin contraception (IPC) dominates contraception usage. There is a lack of robust comparative data on these contraceptive options to inform policy, programs, clinical counseling, and women's choices.

Methods: Within the context of a South African program to increase women's access to the IUD, we conducted a pragmatic, open-label, parallel-arm, randomised controlled trial of the IUD versus IPC at two South African hospitals. The target sample size was 7,000 women and the randomisation ratio was 1:1. The random sequence was computer-generated and group allocation was concealed in sealed, opaque, consecutively-numbered envelopes. Counselled, consenting women attending termination of pregnancy services were randomly assigned to IUD or IPC immediately post-termination. Condoms were promoted for the prevention of sexually-transmitted infections. The primary outcome was pregnancy; secondary outcomes were discontinuation, side-effects, and HIV acquisition and disease progression. Pregnancy and discontinuation outcomes are reported here.

Results: The trial closed early with 2,493 participants randomised (IUD = 1,247, IPC = 1,246), due to international concerns regarding a possible association between IPC and HIV acquisition. Median follow-up was 20 months; 982 and 1000 participants were followed up in the IUD and IPC groups, respectively. Baseline group characteristics were comparable. Pregnancy occurred significantly less frequently among women allocated to the IUD than IPC: 56/971 (5.8 %) versus 83/992 (8.4 %), respectively; risk ratio (RR) 0.69, 95 % confidence interval (CI) 0.50 to 0.96; $P = 0.025$. There were more protocol violations in the IUD group; however, discontinuation rates were similar between IUD and IPC groups (141/855 [16.5 %] and 143/974 [14.7 %], respectively). Women in the IUD group were more likely to discontinue contraceptive use due to abdominal pain or backache and non-specific symptoms, and those in the IPC group due to oligo- or amenorhoea and lack of sexual activity.

(Continued on next page)

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RESEARCH

Effects of injectable progestogen contraception versus the copper intrauterine device on HIV acquisition: sub-study of a pragmatic randomised controlled trial

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ABSTRACT

Background Evidence from observational studies suggests an increased risk of HIV acquisition among women using depot medroxyprogesterone acetate (DMPA) contraception.

Methods Within the context of a South African programme to increase women's access to the intrauterine contraceptive device (IUD), we conducted a pragmatic, open-label, parallel-arm, randomised controlled trial (RCT) of the IUD versus injectable progestogen contraception (IPC) at two South African hospitals. The primary outcome was pregnancy; secondary outcomes included HIV acquisition. Consenting women attending termination of pregnancy services were randomised after pregnancy termination between July 2009 and November 2012. Condoms were promoted for the prevention of sexually transmitted infections. Voluntary HIV testing was offered at baseline and at 12 or more months later. Findings on HIV acquisition are reported in this article.

Results HIV acquisition data were available for 1290 initially HIV-negative women who underwent a final study interview at a median of 20 months after randomisation to IPC or an IUD. Baseline group characteristics were comparable. In the IPC group, 545/656 (83%) of participants received DMPA, 96 (15%) received injectable norethisterone enanthate, 14 (2%) received the IUD and one received oral contraception. In the IUD group 609 (96%) received the IUD, 20 (3%) received IPC and 5 (1%) had missing data. According to intention-to-treat analysis, HIV acquisition occurred in 20/656 (3.0%) women in the IPC arm and 22/634 (3.5%) women in the IUD arm (IPC vs IUD, risk ratio 0.88; 95% confidence interval 0.48–1.59; p=0.7).

Conclusions This sub-study was underpowered to rule out moderate differences in HIV risk, but confirms the feasibility of randomised trial methodology to address this question. Larger RCTs are needed to determine the relative risks of various contraceptive methods on HIV acquisition with greater precision.

Trial registration number Pan African Clinical Trials Registry number PACTR201409000880157 (04-09-2014).

Key message points

- The net physiological and behavioural effects of hormonal contraception on HIV acquisition cannot be predicted from existing animal models and observational clinical data.
- To date there is no evidence from randomised controlled trials (RCTs) which confirms a greater risk with injectable progestogens than with the copper intrauterine device.
- Larger RCTs are needed to determine the relative risks of HIV acquisition with various contraceptive methods.
- Contraception providers should continue to counsel women on the measures available to prevent HIV acquisition.

BACKGROUND

The possibility that hormonal contraception, particularly depot medroxyprogesterone acetate (DMPA), increases HIV

RESEARCH

The effect of depot medroxyprogesterone acetate on postnatal depression: a randomised controlled trial

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ABSTRACT

Background Depot medroxyprogesterone acetate (DMPA) is the most commonly used hormonal contraceptive method in South Africa. It is frequently administered in the immediate postnatal period, yet it is unclear whether it affects the risk of postnatal depression (PND).

Aim To determine whether DMPA increases the risk of PND compared with the copper-containing intrauterine device (IUD) when administered after delivery.

Design and setting A single-blind randomised controlled trial conducted at two teaching hospitals in East London, South Africa.

Methods Eligible, consenting women (*N*=242) requiring postnatal contraception were randomised to receive DMPA or an IUD within 48 hours of childbirth and interviewed at 1 and 3 months postpartum. Depression was measured using the Beck Depression Inventory (BDI-II) and the Edinburgh Postnatal Depression Scale (EPDS). Resumption of sexual intercourse, menstrual symptoms and breastfeeding rates were also assessed.

Results One-month EPDS depression scores were statistically significantly higher in the DMPA arm compared with IUD arm (p=0.04). Three-month BDI-II scores were significantly higher in the DMPA arm than in the IUD arm (p=0.002) and, according to the BDI-II but not the EPDS, more women in the DMPA arm had major depression at this time-point (8 vs 2; p=0.05). There were no statistically significant differences in other outcome measures except that fewer women had resumed sexual activity by 1 month postpartum in the DMPA arm (13% vs 26%; p=0.02).

Conclusions The possibility that immediate postnatal DMPA use is associated with depression cannot be excluded. These findings justify further research with longer follow-up.

Clinical trial number PACTR201209000419241.

Key message points

- Contraception provision in the immediate postnatal period is integral to the success of family planning programmes in South Africa.
- Depot medroxyprogesterone acetate (DMPA) is the most commonly used postnatal contraception option in South Africa but uncertainty remains about several potential side effects, including postnatal depression (PND).
- This study was unable to exclude an association between DMPA and PND and more research is needed.

INTRODUCTION

Globally, approximately two-thirds of postnatal women have an unmet need for family planning.[1] Initiation of injectable progestogen contraception (IPC) before 6 weeks postpartum is not recommended by the World Health Organization (WHO) unless other methods are not available or not acceptable, because of unknown long-term effects on the infant.[2] However, in South Africa, where unplanned pregnancy rates are high,[3] the South African Department of Health does not restrict the use of injectable contraceptives in the postnatal period,[4] and these are routinely offered to women before postnatal discharge from health services.[5 6] IPC is thus the most commonly used postnatal contraceptive method and, in one South African study, 91% of new mothers attending a child health clinic had used an injectable contraceptive after delivery.[5]

BMJ Open

Psychological, behavioural and physiological effects of three long-acting reversible contraception (LARC) methods: protocol for an ancillary study of the ECHO randomised trial

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ABSTRACT

Introduction This is the protocol for an ancillary study to the multicentre Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial, a three-arm randomised trial comparing the effects of depot medroxyprogesterone acetate (DMPA), the levonorgestrel (LNG) implant and the copper intrauterine device (IUD) on HIV incidence (NCT02550067 pre-results). The ancillary study will compare other non-contraceptive effects of these three long-acting, reversible contraceptions about which there is little existing comparative evidence.

Methods and analysis Women randomised to IUD, DMPA and LNG implant (1:1:1) at one of the ECHO trial sites will be asked to participate in the ancillary study at the 1-month follow-up visit. Research staff will interview women that consent to participate at the 3-month follow-up visit. Primary outcomes are depression, sexual dysfunction and menstrual disturbances. The Beck Depression Inventory will be used to assess depression and the Arizona Sexual Experiences Scale to assess sexual dysfunction. Participants will also be asked to prospectively complete a 28-day symptom diary. The required sample size is 522 participants. Depression scores will be analysed as continuous and categorical variables. Analysis will be by intention to treat.

Ethics and dissemination The ancillary study protocol received ethical approval from the University of the Witwatersrand Committee for Research on Human Subjects on 17 February 2016 (reference no. 14112). The results will be disseminated in a peer-reviewed open-access journal.

Trial registration number PACTR201706001651380.

Strengths and limitations of this study

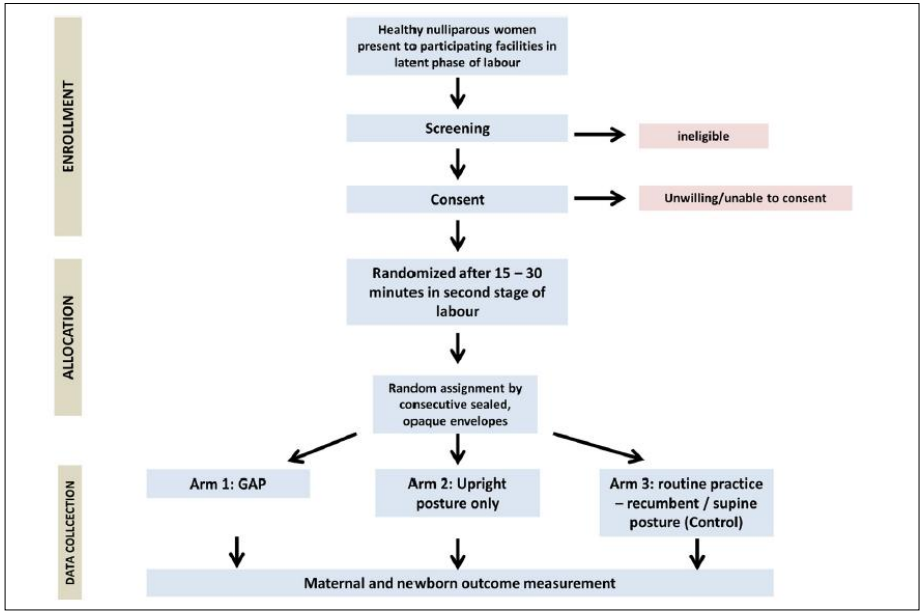
- This ancillary study will compare the effects of three long-acting, reversible contraceptions (LARCs; intrauterine device, depot medroxyprogesterone acetate and levonorgestrel implant) on mood, sexual function, condom use and menstruation, for which there is very little existing evidence. The Evidence for Contraceptive Options and HIV Outcomes trial provides a unique opportunity to compare these non-contraceptive effects of LARCs within the context of a stringent randomised controlled trial protocol.
- While recall bias will be reduced by the use of the daily diary, results will still mostly be based on self-reported data.
- Non-contraceptive effects will be assessed at 3 months after participants are randomised to a LARC, and the lack of longer term follow-up might be a limitation.

INTRODUCTION

There is a need to expand the choice of long-acting, reversible contraception (LARC) for women in low-income and middle-income countries (LMICs) where injectable progestogens, such as depot medroxyprogesterone acetate (DMPA), are often the only LARCs available. In such settings, findings from a Cochrane systematic review suggest that the copper intrauterine device (IUD) is probably more effective than DMPA at preventing pregnancy.[1] However, there remains a lack of robust evidence on non-contraceptive benefits, side effects and HIV risk of different LARC methods that is necessary to inform family planning health policies, contraceptive counselling and the individual woman's contraceptive choice.

Contraception is a complex intervention involving medical, physiological, psychological, behavioural and personal components to which both desirable and undesirable non-contraceptive effects have been attributed. LARCs include various non-hormonal (IUDs) and hormonal options (injections, implants, hormonal IUDs (eg, Mirena)), which quite plausibly have different side effects. Side effects attributed by women to their contraception method often lead

Other Research



Flow chart for the GAP study

Table 3 Birth outcomes

	Routine practice n=384			Upright position n=386			GAP in upright position n=388		
	N	n	%	N	n	%	N	n	%
Final mode of birth									
Spontaneous cephalic	384	367	95.6	386	371	96.1	388	374	96.4
Vaginal breech	384	0	0.0	386	0	0.0	388	0	0.0
Vacuum or forceps	384	4	1.0	386	4	1.0	388	6	1.5
Caesarean section	384	13	3.4	386	11	2.9	388	8	2.1
Reasons for operative birth									
Poor progress	17	4	23.5	15	6	40.0	14	5	35.7
Fetal distress	17	1	5.9	15	1	6.7	14	1	7.1
Other	17	12	70.6	15	8	53.3	14	8	57.1

GAP, gentle assisted pushing.

Source: Hofmeyr et al, 2018

Primary research

The Gentle Assisted Pushing (GAP) Trial

Funded by the World Health Organization, ECRU conducted this open-label, randomized trial with three parallel arms in three Eastern Cape across hospitals (Frere, Cecilia Makiwane and Butterworth Hospitals). The objective was to establish whether upright posture and/or the application of a gentle, controlled fundal pressure technique (GAP) during the second stage of labour could improve birth outcomes.

A total of 1,158 participants took part. The trial showed no clear benefit of the GAP technique, nor of upright posture, on mode of birth. Some women found the upright position uncomfortable, and the study conclusions were that women should be encouraged to assume the posture they find most comfortable. In addition, the use of fundal pressure should be limited to further research designed to determine whether specific techniques of fundal pressure in certain settings may safely assist vaginal birth.

Research Focus: Other Research

Research impact

Findings from the GAP trial have contributed to the evidence bases on, both, birth position and fundal pressure, and support the recent WHO intrapartum care recommendations on these options.

2018 WHO recommendations:

"For women without epidural analgesia, encouraging the adoption of a birth position of the individual woman's choice, including upright birth positions, is recommended."

"Application of manual fundal pressure to facilitate childbirth during the second stage of labour is not recommended."

Source: WHO recommendations: intrapartum care for a positive childbirth experience (2018)

Research

BMJ Global Health

Does gentle assisted pushing or giving birth in the upright position reduce the duration of the second stage of labour? A three-arm, open-label, randomised controlled trial in South Africa

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ABSTRACT

Introduction Gentle assisted pushing (GAP) is an innovative method of applying gentle, steady pressure to a woman's uterine fundus during second stage of labour. This randomised trial evaluated GAP in an upright position, compared with upright position alone or routine practice (recumbent posture).

Methods An open-label, hospital-based, randomised trial was conducted in Eastern Cape, South Africa. Randomisation occurred following at least 15 min in second stage of labour. Participants were randomly assigned (1:1:1) using computer-generated block randomisation of variable size using opaque, sealed, numbered envelopes. Primary analysis was intention to treat. Participants were healthy, nulliparous, consenting women with a singleton pregnancy in cephalic presentation where vaginal birth was anticipated. The primary outcome was mean time from randomisation to birth.

Results 1158 participants were randomly allocated to GAP (n=388), upright position (n=386) and routine practice (n=384), with no loss to follow-up. Baseline characteristics were largely similar. In the experimental arm, GAP was applied a median of two times (IQR 1.0–3.0). Women in upright position alone spent a median of 6 min (IQR 3.0–10.0) upright. Mean duration from randomisation to birth was not different across groups (mean (SD) duration: 24.1 (34.9) min in GAP group, 24.6 (30.5) min in upright group, 25.0 (39.3) min in routine practice group). There were no differences in secondary outcomes, except that at two sites maternal discomfort was greater for both GAP and upright position compared with routine practice; at the other sites there were no differences.

Conclusion No benefit was identified from GAP in the second stage; some women found the position uncomfortable. The use of fundal pressure should be limited to further research to determine techniques or settings in which it can safely assist vaginal birth. Women should be encouraged to assume the position they find most comfortable.

Trial registration number PACTR201502001034448.

Key questions

What is already known?

- Nine trials have been conducted previously on fundal pressure during the second stage of labour compared with no treatment—five trials (3057 women) of manual fundal pressure and four trials (891 women) of fundal pressure by means of an inflatable belt versus no fundal pressure. Most trials had design limitations, and none were able to blind women or staff to allocation.
- There is insufficient evidence to draw conclusions on the beneficial or harmful effects of fundal pressure (either manually or by inflatable belt) for mother or baby.
- Because of current widespread use of fundal pressure in clinical settings, and the potential for use in settings where other methods of assisted birth are not available, further good quality trials are needed to guide practice.

What are the new findings?

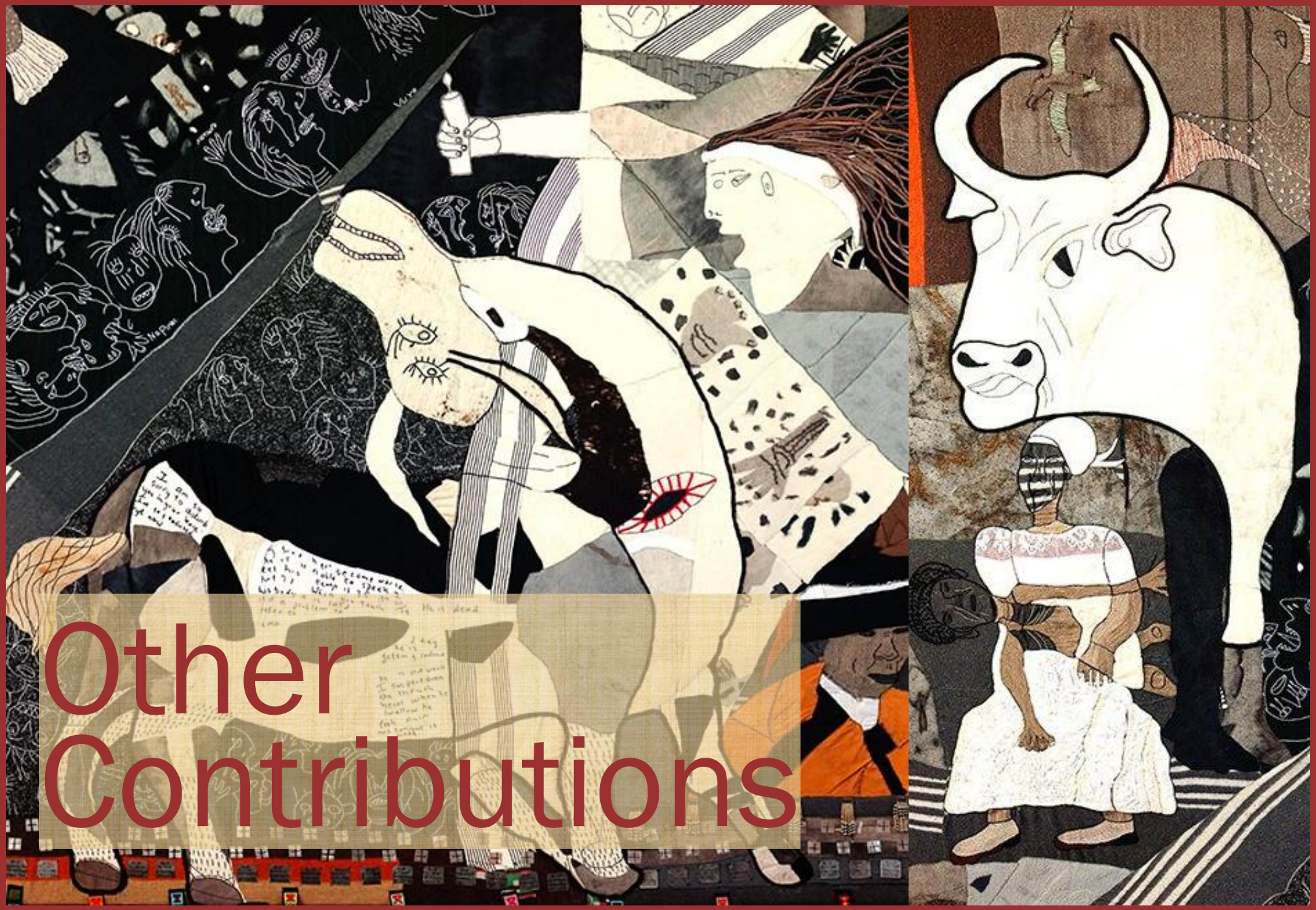
- This trial showed no clear benefit from a new technique of a gentle, controlled form of manual fundal pressure, nor of upright position alone in the second stage of labour. Some women found the upright position (with or without fundal pressure) uncomfortable, although findings were mixed.

What do the new findings imply?

- There is insufficient evidence of effectiveness or safety to support the use of fundal pressure, except in the context of research designed to determine whether specific techniques of fundal pressure in certain clinical situations may be beneficial and safe. Given the lack of clear benefits of specific postures in the second stage of labour, women may be encouraged to use the posture they find most comfortable.

BACKGROUND

Applying manual fundal pressure to expedite birth was originally described by Samuel



Other Contributions

Other Contributions

Effective Care Research Unit

In addition to research and capacity building, ECRU has contributed to advocacy and health service implementation in the Eastern Cape and South Africa by:

- Developing ***Guidelines for Obstetric Care*** in a booklet distributed by the Eastern Cape Department of Health.
- Conducting workshops throughout the Eastern Cape for implementation of the ***National Prevention of Mother To Child Transmission of HIV Program.***

ECRU has also developed teaching videos for practical guidance on certain obstetric procedures. These are freely available in the WHO Reproductive Health Library (https://extranet.who.int/rhl) and on YouTube.

Teaching videos published in the WHO Reproductive Health Library include:

- External Cephalic Version: Why and How?
- Labour Companionship: Every Woman's Choice
- Steps to Overcome Shoulder Dystocia
- Umbilical Vein Injection for Retained Placenta: Why and How?
- Vaginal Breech Delivery and Symphysiotomy
- Vacuum Extraction
- Caesarean Section Evidence-Based Surgical Technique

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