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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.
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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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Blood transfusion was used less frequently in the misoprostol group, although this might have been a chance occurrence. Alternatively, there might be a synergistic pharmacologic effect between misoprostol and conventional uterotonics, which were given to most women with higher levels of blood loss. Indeed, many women in the misoprostol group received both misoprostol and conventional uterotonics, whereas those in the oxytocin group received only conventional oxytocics.

A pharmacokinetic study linked to the WHO trial showed a longer time to peak serum levels of misoprostol (20–30 minutes) compared with oxytocin (3 minutes) [10]. This difference might account for the higher levels of earlier postpartum blood loss observed with misoprostol [10]. Physiologic studies have also shown a more rapid onset of uterine contractions after syntometrine than after misoprostol administration following birth [11]. These findings do not exclude the possibility that misoprostol might have a beneficial effect on more persistent bleeding.

On the basis of a systematic review of pharmacokinetic, physiologic, and clinical studies of misoprostol, the sublingual route of administration shows the greatest promise (rapid onset, highest peak, and long duration) [12]. A systematic review of data from randomized clinical trials using direct and adjusted indirect comparisons found no evidence that 600 μg of misoprostol has a greater effect than 400 μg [13]. For this reason, a sublingual dose of 400 μg of misoprostol was chosen in the present study.

Misoprostol has been recommended for the prevention of PPH when other methods are not available [14,15]. The aim of the present trial was to assess the safety of misoprostol and to determine whether sublingual administration of a 400-μg dose could augment the effectiveness of current routine active management of the third stage of labor in reducing postpartum blood loss.

2. Materials and methods

The present hospital-based, multicenter, randomized, placebo-controlled, double-blind trial was a collaboration among the Effective Care Research Unit (East London, South Africa), Gynuity Heath Projects (New York, USA), and 4 hospital services: Dora Nginza Hospital and Rob Ferreira Hospital in South Africa; Mulago Hospital in Uganda; and University College Hospital in Nigeria. The trial was conducted from March 6, 2006, to August 13, 2007. The 4 hospitals received local ethics approval before recruitment began. The trial is reported according to the CONSORT statement [16].

Women without significant obstetric complications who expected to give birth vaginally were invited to participate and were provided with information about the trial during prenatal care or on admission for delivery. Eligible consenting women were asked to sign or thumbprint a written informed consent if they agreed to participate. All of the participating women received routine prevention and, if needed, treatment for PPH, and good clinical practice procedures were followed. The following women were excluded from the study: those who delivered via cesarean or had an assisted vaginal birth; those in whom sublingual administration of misoprostol was not possible; those in whom the pregnancy was not viable according to local gestational viability age limits; those who declined, or were too ill or distressed, to give consent; and those not entitled to give informed consent, such as minors.

In all centers, study drug pack dispensers were placed in a central location on a research trolley close to the delivery beds. When a participant enrolled, the researcher took the next study drug pack from the dispenser and immediately wrote the woman's name both on the pack and in the participant number list, which was kept separate from the case record forms. Enrollment took place when the pack was removed from the pack dispenser. The pack could not be used for another woman or returned to the dispenser. The random allocation sequence was generated by using computer-generated random numbers and was stratified by country in blocks of 6–8. The trial medication was provided, and the study drug packs were prepared, by Gynuity Health Projects. The packs were identical in shape, color, weight, and feel, and contained either 2 tablets of 200 μg of misoprostol (HRA Pharma, Paris, France) or 2 matching placebo tablets. Women who enrolled in the trial received 400 μg of misoprostol or placebo immediately after delivery, in addition to standard active management of the third stage of labor, as currently practiced in the collaborating centers (parenteral oxytocin in Uganda and South Africa, and oxytocin or ergometrine in Nigeria).

The study followed the blood loss measurement method described in the WHO trial of misoprostol for the prevention of PPH [9]. Blood collection was started as soon as possible after delivery. A fresh, non-absorbent sheet was placed under the buttocks of the woman. A low-profile, plastic "fracture" bedpan was positioned below the woman's perineum in a position to collect all subsequent blood loss, for a period of 1 hour, measured by a standard clock. The blood collected in the bedpan and any spilled blood, which was collected from the non-absorbent sheet and any blood-soaked small gauze swabs, were transferred to a measuring jar and the volume was measured. Alternatively, the blood was collected into a plastic sheet placed below the woman immediately after delivery. If excessive bleeding had not stopped at the end of the measured 1-hour collection, the collection was restarted and additional blood loss was measured until the bleeding had subsided. Attempts were made to minimize blood loss on the drapes and on the gowns of the attendant during delivery. In addition, the placental interstices also contain maternal blood (approximately 9% of the placental weight). Because overestimations (amniotic fluid) and underestimations (blood loss) were likely to be distributed equally between the 2 study groups, and most would have occurred before the onset of measurement, the data were not corrected. Because longer-term blood loss measurement is more difficult to standardize, the outcome was based on blood measured in the first hour after delivery.

The baseline characteristics of the women were recorded to assess whether the study groups were comparable at trial entry. Adverse effects were recorded by the researcher as they were observed or reported in response to direct questioning. The primary outcome was the incidence of 500 mL or more of measured blood loss within 1 hour after the trial medication was administered. Secondary outcomes were the mean measured blood loss 1 hour after the trial medication was administered, a measured blood loss of 1000 mL or more, adverse effects such as shivering (mild and moderate/severe) and pyrexia, manual removal of the placenta, laparotomy, hysterectomy, and maternal morbidity and mortality.

In 2 WHO trials [8,9], the incidence of a measured blood loss of 500 mL or more in the injectable oxytocic group was 13.8%. To show a reduction to 8.5% with 95% certainty and 80% power would require 1180 women (Epi Info software, Centers for Disease Control and Prevention, US Department of Health and Human Services). Data were analyzed and reported on an intention-to-treat basis, and comparisons were made between sublingual misoprostol and placebo. The analysis plan was finalized before recruitment started.

Data were collected prospectively by researchers at the local collaborating centers, and data checking and entry of the completed data collection forms and initial analyses were undertaken at each local center. This decentralized data management contributed to the capacity-building objective of the study. Data were collected on paper forms, transferred to Excel (Microsoft, Washington, USA), checked for accuracy, and analyzed using Epi Info software, except for the mean differences, which were analyzed by RevMan version 5.0 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Duplicate copies of the original data collection forms were sent to the coordinating center for quality-control purposes. Quality control by the coordinating center included checking Excel spreadsheets and finalizing all queries before the randomization code was provided by Gynuity Health Projects. Serious adverse events were reported by the local investigators to the trial coordinator within 24 hours of the event.

Because of the decentralized model used, the data from the participating centers were combined by meta-analysis using RevMan version 5.0. This enabled an exploration of any discrepancies among the results from different sites, and the use of a random effects model in the event of heterogeneity resulting from differences among the study sites. In the absence of heterogeneity, the results were combined by using a fixed-effects model.

3. Results

The present hospital-based, decentralized, multicenter, randomized, placebo-controlled, double blind study aimed to enroll 1180 women. Not all sites were able to achieve their allocated number, and a total of 1103 women had been enrolled at the close of the trial (Fig. 1). Women were randomized to receive either 400 μg of misoprostol sublingually (547 women) or placebo (556 women), in addition to routine injectable uterotonics, immediately after delivery as part of active management of the third stage of labor. The denominators in Tables 1 and 2 indicate the numbers of women for whom data were available. Data for the primary outcome were not available for 4 of the 1103 women. The 2 groups were similar in terms of baseline characteristics, except for a 2.8-year difference in mean age (Table 1).

There was no significant difference in the primary outcome, defined as blood loss of 500 mL or more within 1 hour of administration of the trial medication (relative risk [RR], 0.64; 95% confidence interval [CI], 0.38–1.07), which occurred in 22/546 (4.03%) women allocated to misoprostol and in 35/553 (6.33%) women allocated to placebo. There was no significant heterogeneity observed among the trial sites ($I^2 = 0\%$).

Table 1
Baseline data of participants.[a]

	Misoprostol		Placebo	
	n		n	
Age, y	547	25 ± 5.6	556	28 ± 6.0
Primiparous	543	145 (26.70)	553	146 (26.40)
Labor induced with misoprostol	476	24 (5.04)	479	24 (5.01)
Placenta delivered before trial tablets taken	544	127 (23.34)	554	123 (22.20)

[a] Values are given as mean ± SD or number (percentage).

There was no significant difference in mean blood loss occurring within 1 hour of taking the tablets (weighted mean difference, −9.58; 95% CI, −22.3 to 3.14), or in the incidence of blood loss of 1000 mL or more (RR, 3.70; 95% CI, 0.61–22.4).

Shivering occurred in 142/544 women and 67/556 women in the misoprostol and the placebo groups, respectively (average RR [random effects model], 2.14; 95% CI, 1.24–3.70); however, there was significant heterogeneity among the sites ($I^2 = 58\%$), and thus it is possible that shivering was inconsistently reported at the trial sites. Moderate to severe shivering occurred in 30/377 women in the misoprostol group and 13/381 women in the placebo group (RR, 2.34; 95% CI, 1.25–4.39). Pyrexia of more than 37.5 °C was more common in the misoprostol group (RR, 2.24; 95% CI, 1.48–3.41). Pyrexia of more than 39 °C was uncommon and reported mainly at 1 site (Nigeria).

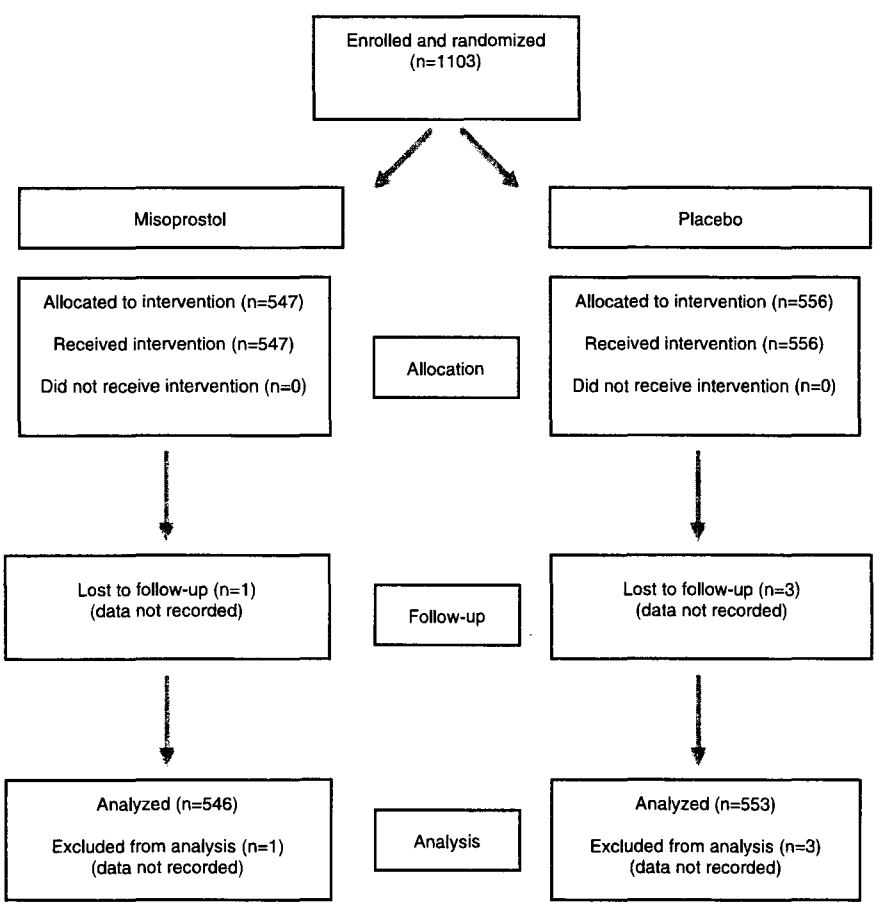

Fig. 1. Flow of participants through the study.

Table 2
Outcomes of the trial.[a]

Outcomes	Misoprostol		Placebo		RR/WMD (95% CI) [b]	I^2, % [c]
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)	0
Secondary						
Mean blood loss within 1 h after taking trial tablets, mL	540	189	549	199	−9.58 (−22.3 to 3.14)	0
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)	0
Mild shivering	544	142 (25.6)	556	67 (12.1)	2.14 (1.25–3.70)	58
Moderate to severe shivering	377	30 (8.0)	381	13 (3.4)	2.34 (1.25–4.39)	0
Pyrexia ≥ 37.5 °C	522	61 (11.7)	536	28 (5.2)	2.24 (1.48–3.41)	0
Pyrexia ≥ 39 °C	521	8 (1.5)	536	1 (0.2)	2.60 (0.05–136.8)	71
Manual removal of placenta	446	32 (7.2)	455	33 (7.3)	0.98 (0.62–1.55)	0
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] I^2 indicates heterogeneity between the sites.

Severe morbidity was rare. There were 4 laparotomies in the misoprostol group and 5 in the placebo group, and 1 hysterectomy in the misoprostol group. No maternal deaths occurred during the trial.

4. Discussion

The present trial used a novel decentralized method to maximize the capacity-development aspect of the study and to reduce the costs associated with centralized data management.

The occurrence of the primary outcome in the placebo group was considerably lower (6.3%) than the estimate used for the power calculation; as a result, the trial was powered to detect only a large (60%) reduction (6.3%–2.5%). The present results are consistent with those of 2 previous trials, which included a comparison of 400 μg of misoprostol administered rectally [17] or orally [18] plus oxytocin versus placebo plus oxytocin for the prevention of PPH, and those of 1 concurrent trial also coordinated by the Effective Care Research Unit [19]. The 2 previous trials were identified from a systematic review of randomized trials of misoprostol for the prevention or treatment of PPH [13]. Meta-analysis of data from the 4 trials, using RevMan version 5.0, showed a significant reduction in the incidence of blood loss of 500 mL or more (4013 women [RR, 0.75; 95% CI, 0.58–0.96]; Fig. 2), and a trend toward a lower incidence of blood loss of 1000 mL or more (4013 women [RR, 0.68; 95% CI, 0.41–1.11]; Fig. 3).

The present trial confirmed the finding of previous studies of increased shivering and pyrexia in the misoprostol group [8,9,13]. As in previous studies of misoprostol doses less than 600 μg, no cases of hyperpyrexia (>40 °C) were observed. The present study showed an apparent geographic variation in susceptibility to misoprostol-induced pyrexia. Pyrexia of more than 39 °C in the misoprostol group occurred in 8/164 (4.9%) women in Nigeria, and no women in South Africa or Uganda. In a recent report, hyperpyrexia (<40 °C) after the administration of 800 μg sublingual misoprostol for treatment of PPH occurred in 36% of women in Ecuador, compared with 2%–9% of women at 2 hospitals in Vietnam and 0% of women in Egypt [20,21].

This information is an important addition to ongoing research into the relative benefits and adverse effects of misoprostol administration in different dosages, by various routes, and with different co-interventions in the prevention of PPH. With regard to clinical practice, the relatively small benefit (a reduction in PPH from approximately 7% to 4%–5%) is probably outweighed by the shivering and fever exhibited after adjunct prophylaxis with misoprostol. Given the established benefits of oxytocin alone over misoprostol alone for PPH prophylaxis, our research found inadequate evidence to support adjunct use of misoprostol when oxytocin prophylaxis is available. Further research

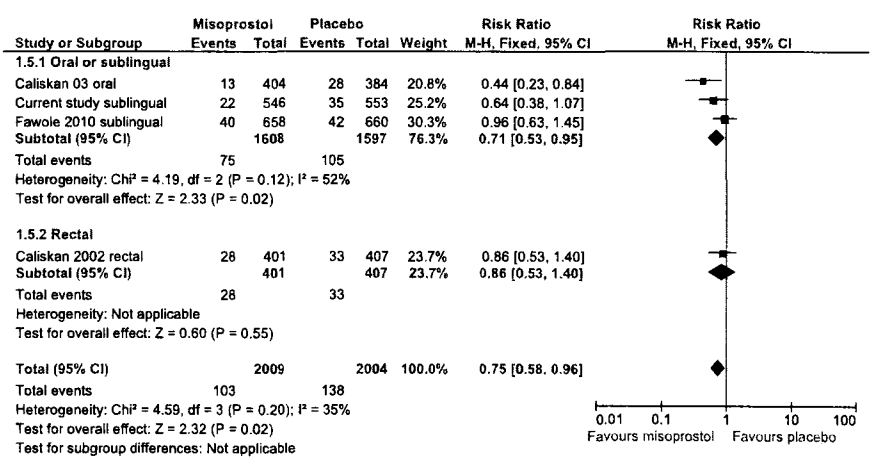

Fig. 2. Incidence of postpartum hemorrhage (PPH) after prophylaxis with misoprostol. Shown is a meta-analysis of all trials (including the current trial) [17–19] assessing the effects of the administration of 400 μg of misoprostol versus placebo, in addition to routine uterotonics. PPH was defined as measured blood loss of 500 mL or more within 1 hour of taking misoprostol or placebo.

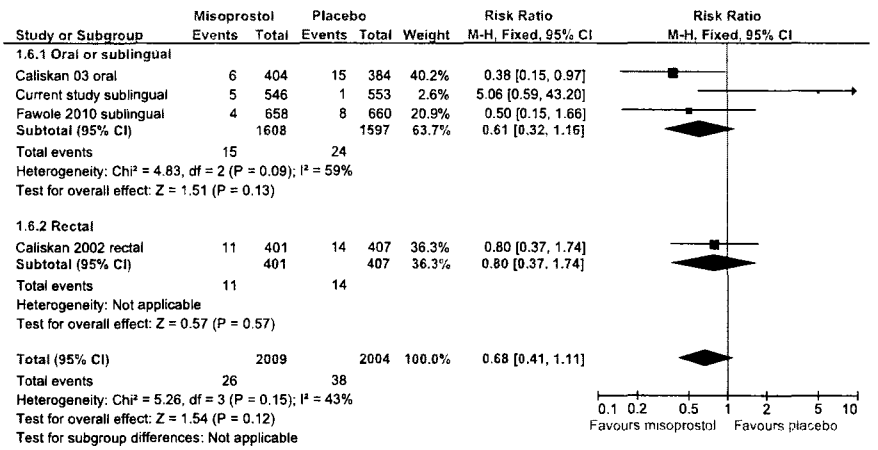

Fig. 3. Incidence of severe postpartum hemorrhage (PPH) after prophylaxis with misoprostol. Shown is a meta-analysis of all trials (including the current trial) [17–19] assessing the effects of the administration of 400 μg of misoprostol versus placebo in addition to routine uterotonics. Severe PPH was defined as a measured blood loss of 1000 mL or more within 1 hour of taking misoprostol or placebo.

in settings where injectable uterotonics are not available should determine the optimal misoprostol regimen to achieve the greatest benefit-to-risk ratio.

The findings of the present trial are not conclusive. However, meta-analysis indicates a moderate reduction in the incidence of postpartum blood loss of more than 500 mL when 400 μg of misoprostol is given in addition to routine active management with oxytocin. In places where routine uterotonics are available, the potential small benefit of administering misoprostol in addition to standard uterotonics as PPH prophlaxis might not outweigh the likelihood of adverse effects.

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Conflict of interest

The authors have no conflicts of interest.

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CLINICAL ARTICLE

A double-blind, randomized, placebo-controlled trial of misoprostol and routine uterotonics for the prevention of postpartum hemorrhage

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ABSTRACT

Objective: To assess the effects of 400-μg sublingual misoprostol plus routine uterotonics on postpartum hemorrhage. *Methods:* A double-blind, placebo-controlled, randomized study was performed. After delivery of the child, eligible women received routine uterotonics and were randomly allocated to receive 400-μg misoprostol or placebo sublingually. The primary outcome measure was blood loss of at least 500 mL within 1 hour of taking the trial tablets. *Results:* In total, 672 women received misoprostol and 673 received placebo. The baseline data were similar for both groups. Misoprostol plus routine uterotonics reduced postpartum blood loss, but the effect was not significant for blood loss of at least 500 mL (relative risk [RR] 0.96; 95% confidence interval [CI], 0.63–1.45) or blood loss of at least 1000 mL (RR 0.50; 95% CI, 0.15–1.66). Misoprostol also reduced the need for non-routine oxytocin, manual removal of the placenta, and hysterectomy, but these differences were not significant either. Misoprostol was associated with pyrexia and moderate/severe shivering. There was no death in either group. *Conclusion:* Misoprostol plus routine uterotonics resulted in modest reductions of blood loss in the third stage of labor, but the effects did not reach statistical significance. Larger studies are recommended.
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1. Introduction

Postpartum hemorrhage is the most common cause of maternal mortality. More than one-third of all maternal deaths in Africa and Asia, where most maternal deaths occur, result from this complication [1]. Most cases of postpartum hemorrhage are, in turn, caused by uterine atony, which is preventable. Thus, postpartum hemorrhage and the associated maternal deaths can essentially be averted.

In light of the global concern to improve women's health and reduce maternal mortality, initiatives have promoted active management of the third stage of labor—an evidence-based intervention for the prevention of postpartum hemorrhage—for all deliveries [2,3]. A major component of active management of the third stage of labor is the administration of a prophylactic uterotonic agent [4]. Available evidence supports the routine administration of oxytocin [5] or ergot alkaloids [6] for the prevention of postpartum hemorrhage.

Misoprostol—a prostaglandin E_1 analog with uterotonic properties—has also increasingly been used for obstetric and gynecologic indications within the past 2 decades. Its characteristics (low cost, ease and multiple routes of administration, and thermal stability) have led to expectations that it might be the ideal uterotonic agent for low-income countries. Misoprostol is superior to placebo for the prevention of postpartum hemorrhage [7,8], but is less effective when compared with conventional injectable uterotonics [9–11]. This has informed the recommendation that misoprostol, administered soon after the birth of the child, be used in situations where oxytocin is not available or where skills for administering parenteral drugs are limited [7,8,12].

With a view to minimizing adverse effects and improving efficacy, various uterotonic regimens have been compared. The combination of oxytocin and ergometrine has been shown to be more effective than oxytocin alone [13]. However, ergometrine can induce vomiting and is contraindicated in hypertension.

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It is biologically plausible that misoprostol might also augment the effectiveness of conventional uterotonics. Turkish investigators reported that misoprostol combined with oxytocin was superior to misoprostol or oxytocin alone in preventing postpartum hemorrhage [14,15]. Moreover, combined treatment with misoprostol and oxytocin reduced the need for additional oxytocin or blood transfusions.

The present study was designed to test the hypothesis that 400-μg misoprostol administered sublingually might augment the effectiveness of current routine uterotonics used in active management of the third stage of labor.

2. Materials and methods

The present study was a multicenter, double-blind, placebo-controlled trial implemented concurrently in 6 hospitals in Nigeria: National Hospital, Abuja; Federal Medical Centre, Abeokuta; LAUTECH Teaching Hospital, Osogbo; R-JOLAD Hospital, Lagos; Adeoyo Maternity Hospital, Ibadan; and St Mary's Catholic General Hospital, Ibadan.

Pregnant women were eligible for inclusion in the study if they were expected to deliver vaginally. They were enrolled on admission to the labor ward of participating hospitals. To minimize the risk of blood loss from perineal trauma, only multiparous women were recruited because they were more likely to proceed to normal delivery. Exclusion criteria included any severe allergic condition or severe asthma, age below 18 years, temperature above 38 °C, or abortion of the pregnancy.

The third stage of labor was managed according to the routine in each center, all of which had a policy of active management of the third stage of labor involving the intramuscular or intravenous administration of either 10-IU oxytocin or 0.25-mg/0.5-mg ergometrine immediately after delivery of the child.

In addition to the uterotonic, the participants received 2 tablets of either misoprostol or placebo immediately after delivery. Treatment was allocated in blocks of 6–8 women by the research nurse, who used a computer-generated randomization sequence. The trial drugs were concealed in sealed, sequentially numbered opaque envelopes and were identical in shape, color, size, and design.

Misoprostol was available as Cytotec 200 μg (Pfizer, Madrid, Spain). The 400-μg dose was chosen because maternal deaths have been reported in studies using more than 600 μg of misoprostol, whereas no difference in effect size was observed between the 400-μg and the 600-μg doses of the agent [16]. Misoprostol was administered via the sublingual route, which is superior to oral and rectal administration [17] and is associated with rapid absorption, prolonged duration of action, and the greatest total bioavailability when compared with other routes of administration.

The primary outcome measure was blood loss of at least 500 mL within 1 hour of administration of the trial medication. Secondary outcome measures were total severe postpartum blood loss (measured blood loss of at least 1000 mL within 1 hour of administration of the trial medication), average blood loss 1 hour after administration of the trial drug, need for additional oxytocin or ergometrine, maternal morbidity, maternal mortality, and adverse effects.

Postpartum blood loss was measured as previously described [10]. Blood collection was initiated as soon as possible after administration of the trial medication. A low-profile plastic fracture bedpan was placed below the woman's perineum to collect all subsequent blood loss for a period of 1 hour. Blood collected in the bedpan and all blood-soaked small gauze swabs were emptied into a plastic measuring jar and the volume was measured.

Severe maternal morbidity was defined as a hemoglobin (Hb) concentration below 6 g/dL 24 hours after delivery, receipt of a blood transfusion, manual removal of the placenta, or receipt of a hysterectomy.

Adverse-effect measures were self-reported moderate/severe shivering and pyrexia (body temperature at least 38 °C) within 1 hour of taking the trial drug. The occurrence of nausea, vomiting, and diarrhea after administration of the trial drug was also assessed.

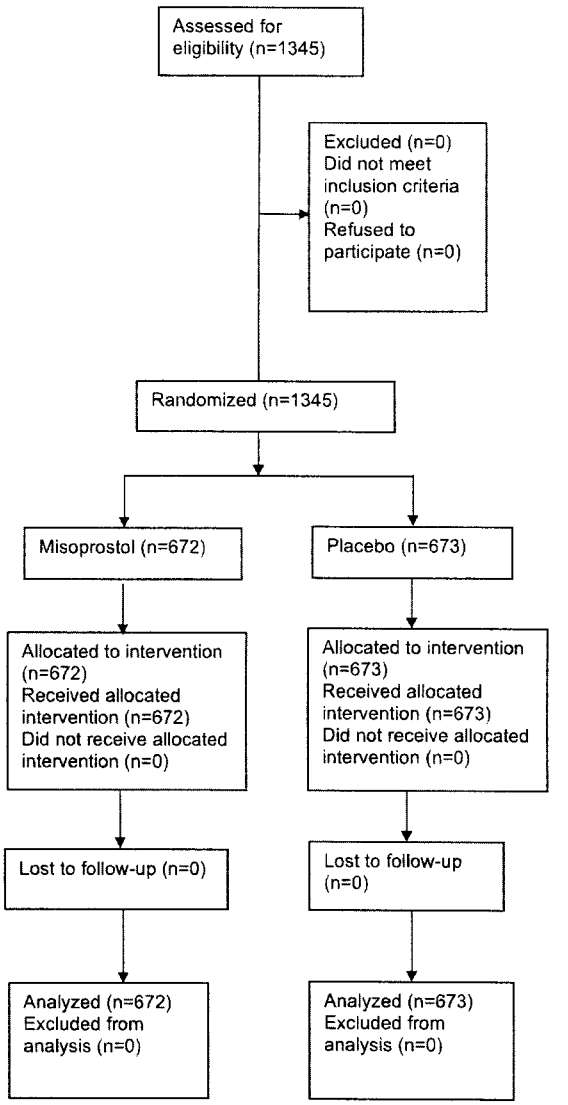

Fig. 1. Flow of participants.

A reduction in postpartum hemorrhage (measured blood loss of at least 500 mL) from 14% for oxytocin to 8.5% for oxytocin plus misoprostol was projected, as reported by Gülmezoglu et al. [10]. The minimum sample size per arm required to achieve 80% power for

Table 1
Baseline characteristics of the participants.[a]

Characteristic	Misoprostol (n = 672)	Placebo (n = 673)
Age, y [b]	31.63 ± 4.50	31.68 ± 4.60
Parity		
Para 1	163 (24.4)	187 (28.0)
Para 2–4	455 (68.2)	441 (66.1)
Grand multipara	49 (7.4)	39 (5.9)
Mean parity [c]	2.42 ± 1.30	2.40 ± 1.30
Labor induced with misoprostol	34 (5.2)	29 (4.5)
Routine uterotonic		
Oxytocin	173 (41.9)	141 (36.6)
Ergometrine	488 (78.3)	495 (78.8)
Birth weight, g [d]	3.27 ± 0.57	3.27 ± 0.51

[a] Values are given as number (percentage) or mean ± SD.
[b] n = 666 in the misoprostol group and n = 671 in the placebo group.
[c] n = 667 in each group.
[d] n = 660 in the misoprostol group and n = 657 in the placebo group.

Table 2
Study outcomes.[a]

Outcomes	Misoprostol	Placebo	Relative risk (95% CI)
Primary			
Blood loss ≥500 mL	40/658 (6.08)	42/660 (6.36)	0.96 (0.63–1.45)
Secondary			
Total blood loss ≥1000 mL	4/658 (0.61)	8/660 (1.21)	0.50 (0.15–1.66)
Mean blood loss 1 hour after administration of trial tablet, mL [b]	211.8 ± 204.7	217.5 ± 201.5	–
Median blood loss 1 hour after administration of trial tablets, mL [b]	150.0 (100.0–250.0)	150.0 (110.0–250.0)	–
Additional oxytocin	76/310 (24.52)	84/324 (25.93)	0.95 (0.72–1.24)
Additional ergometrine	80/343 (23.32)	79/353 (22.38)	1.04 (0.79–1.37)
Hb <6 g/dL 24 h after delivery or blood transfusion	4/665 (0.60)	5/668 (0.75)	0.80 (0.22–2.98)
Manual placenta removal	23/661 (3.48)	27/667 (4.05)	0.86 (0.50–1.48)
Hysterectomy	1/665 (0.15)	2/661 (0.30)	0.50 (0.05–5.47)
Any shivering	172/658 (26.14)	52/655 (7.94)	3.29 (2.46–4.40)
Moderate/severe shivering	44/658 (6.69)	11/655 (1.68)	3.98 (2.07–7.64)
Temperature >38 °C	37/616 (6.00)	12/618 (1.94)	2.97 (1.57–5.65)

Abbreviations: CI, confidence interval; Hb, hemoglobin.
[a] Values are given as number (percentage), mean ± SD, or mean (interquartile range) unless otherwise indicated.
[b] n = 657 in the misoprostol group and n = 660 in the placebo group.

a 2-sided comparison at the 95% certainty level was calculated to be 575, resulting in a total minimum sample size of 1150.

Ethics approval was obtained from the ethics committees of all hospitals involved. Written informed consent was obtained from each participant. Throughout the study, good clinical procedures were followed.

Excel 2003 (Microsoft, Redmond, WA, USA) was used for data entry, and the analyses were performed with Epi Info version 3.5.1 (Centers for Disease Control and Prevention, Atlanta, GA, USA). Relative risk (RR) and 95% confidence interval (CI) were calculated to estimate the treatment effect on outcome measures. Heterogeneity among the hospitals for the main outcome measures was assessed using RevMan 5 (Cochrane Collaboration, Oxford, UK) and was considered significant if I^2 was greater than 50%. All analyses were based on the intention-to-treat principle.

3. Results

The study was conducted between January 1, 2007, and September 30, 2008. In total, 1345 women were recruited: 672 women received misoprostol and a routine uterotonic; and 673 women received placebo and a routine uterotonic. Fig. 1 shows the flow of participants through the study. The baseline characteristics in the 2 arms of the study were similar with regard to age, proportion of primiparous women, proportion of labors induced with misoprostol, type of routine uterotonic administered, and birth weight of the infant (Table 1).

The study outcomes are shown in Table 2. The rate of postpartum hemorrhage (measured blood loss of at least 500 mL 1 hour after taking the trial tablets) was marginally higher in the placebo group (42 [6.36%]) than in the misoprostol group (40 [6.08%]). This difference was, however, not statistically significant (RR 0.96; 95% CI, 0.63–1.45). The rate of total blood loss of at least 1000 mL was also slightly higher among women who received placebo (8 [1.21%]) than among women given misoprostol (4 [0.61%]), but the difference was not statistically significant (RR 0.50; 95% CI, 0.15–1.66). Additional oxytocin was required by 76 (24.52%) women in the misoprostol group and by 84 (25.93%) in the placebo group; the difference was not statistically significant (RR 0.95; 95% CI, 0.72–1.24). Additional ergometrine was required by 80 (23.32%) women in the misoprostol arm and by 79 (22.38%) women in the placebo arm; again, the difference was not statistically significant (RR 1.04; 95% CI, 0.79–1.37). There was also no significant difference in the frequency of manual removal of the placenta: 23 (3.48%) women in the misoprostol group and 27 (4.05%) women in the placebo group (RR 0.86; 95% CI, 0.50–1.48).

One woman (0.15%) in the misoprostol group and 2 (0.30%) women in the placebo group had a hysterectomy (RR 0.50; 95% CI, 0.05–5.47). The difference was not statistically significant. An Hb value below 6 g/dL or blood transfusion was reported for 4 (0.60%) women who received misoprostol and for 5 (0.75%) women who received placebo. The difference was also not statistically significant (RR 0.8; 95% CI, 0.22–2.98). No maternal deaths were reported in either group.

To strengthen the present findings and to indicate where research should be focused, data from the present study were combined with data from 2 similar studies from Turkey [14,15]. In the combined analysis, the addition of misoprostol to a uterotonic resulted in a 24% reduction in the prevalence of postpartum hemorrhage (blood loss of at least 500 mL). However, the result was not statistically significant (RR 0.76; 95% CI, 0.50–1.15) (Fig. 2). There was a significant reduction (of 44%) in the prevalence of severe postpartum hemorrhage (blood loss of at least 1000 mL) when misoprostol was added to a uterotonic (RR 0.56; 95% CI, 0.33–0.95) (Fig. 3). The need for additional oxytocin and ergometrine was reduced by 34% (RR 0.66; 95% CI, 0.39–1.13) and 30% (RR 0.70; 95% CI, 0.33–1.47), respectively. These changes were not statistically significant (Figs. 4 and 5). It should be noted that the combined data for blood loss of at least 500 mL and the need for additional uterotonics showed significant heterogeneity.

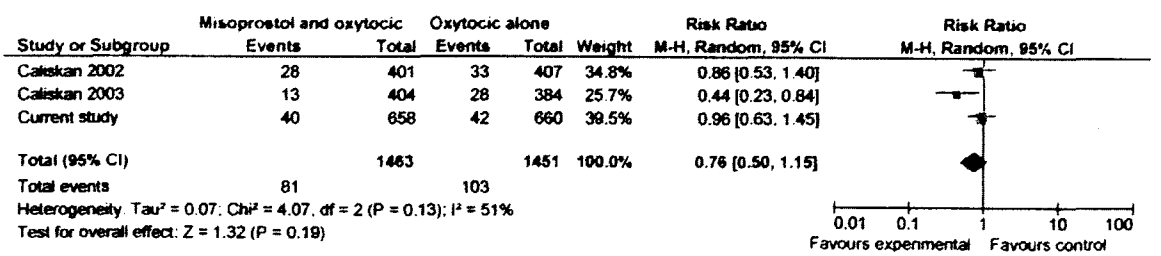

Fig. 2. Blood loss of at least 500 mL. Results of the combined analysis.

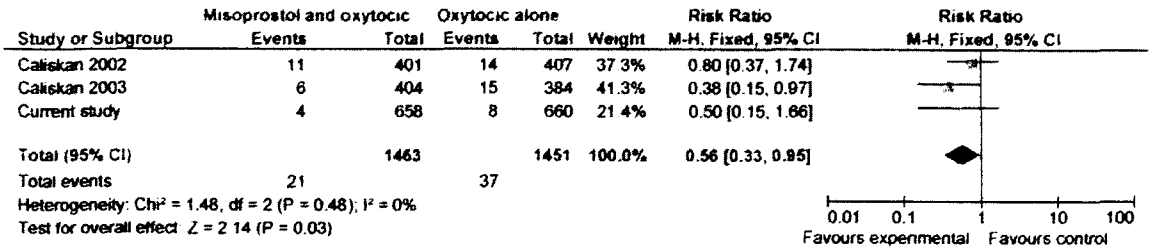

Fig. 3. Blood loss of at least 1000 mL. Results of the combined analysis.

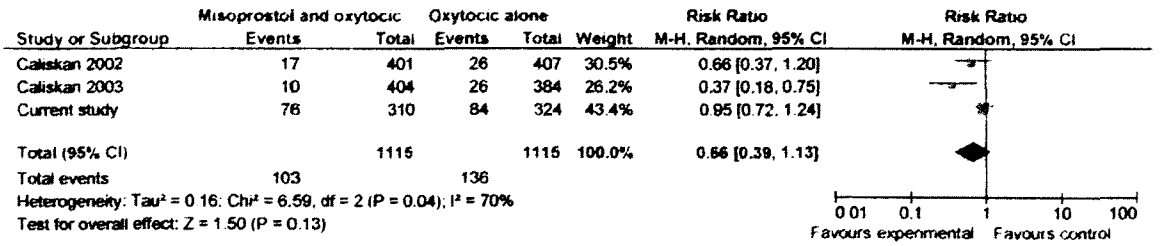

Fig. 4. Need for additional oxytocin. Results of the combined analysis.

Adverse effects were significantly more common with misoprostol (Table 2). "Any shivering" was experienced by more than a quarter (172 [26.14%]) of all women who received misoprostol, compared with only 52 (7.94%) women who received placebo. In most instances, however, the shivering was mild. Moderate/severe shivering occurred in 44 (6.69%) women who received misoprostol and 11 (1.68%) women who received placebo (RR 3.98; 95% CI, 2.07–7.64). Pyrexia was reported by 37 (6.00%) women who received misoprostol and by 12 (1.94%) women who were given placebo (RR 2.97; 95% CI, 1.57–5.65). Shivering and pyrexia resolved spontaneously in all women, without the need for treatment. Nausea, vomiting, and diarrhea were infrequent.

There was no significant heterogeneity (i.e. I^2 was below 50%) in any of the reported outcome events across the 6 study sites, indicating that the results were consistent across all centers. A forest plot showing the trend across hospitals for blood loss of at least 500 mL is displayed in Fig. 6.

4. Discussion

In the present trial, misoprostol given in addition to routine uterotonics as a component of active management of the third stage of labor showed small but insignificant improvements over placebo for most outcomes considered. The prevalence of the primary outcome measure was slightly higher among women who received placebo. A similar trend was observed for severe postpartum hemorrhage. These findings are consistent with data from Turkey [14,15].

Women in the misoprostol arm also tended to have reduced requirements for additional oxytocin, manual removal of the placenta, blood transfusion, and hysterectomy. Caliskan et al. [14] reported similar results. However, they also demonstrated that combined oxytocin and ergometrine were superior to combined oxytocin and misoprostol in preventing postpartum hemorrhage and reducing the need for additional oxytocin.

Shivering and pyrexia were the most commonly reported adverse effects of misoprostol in the present study, as observed by others [18,19]. However, these effects were self-limiting. The relative infrequency of nausea, vomiting, and diarrhea noted in the present study supports the contention that these adverse effects are not commonly associated with the 400-μg dose of misoprostol [20].

A combined analysis of the present data with those from Turkey confirmed that misoprostol given in addition to a uterotonic might confer advantages such as protection from severe postpartum hemorrhage and a reduced need for non-routine oxytocin. These findings require further investigation.

Most previous trials of misoprostol for active management of the third stage of labor have evaluated the drug as an alternative to conventional uterotonics. Systematic reviews of randomized trials have, however, shown that injectable uterotonics are more effective than misoprostol at preventing postpartum hemorrhage [20,21].

Trials that evaluated the adjunctive use of misoprostol with oxytocin have focused mainly on the treatment [18,19,22–24], rather than the prevention [14,15], of postpartum hemorrhage. However, all these reports indicate that misoprostol confers benefit when the woman has previously received, or concurrently receives, conventional uterotonics.

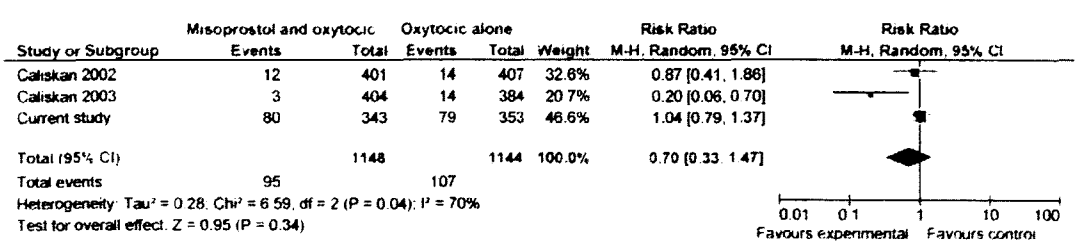

Fig. 5. Need for additional ergometrine. Results of the combined analysis.

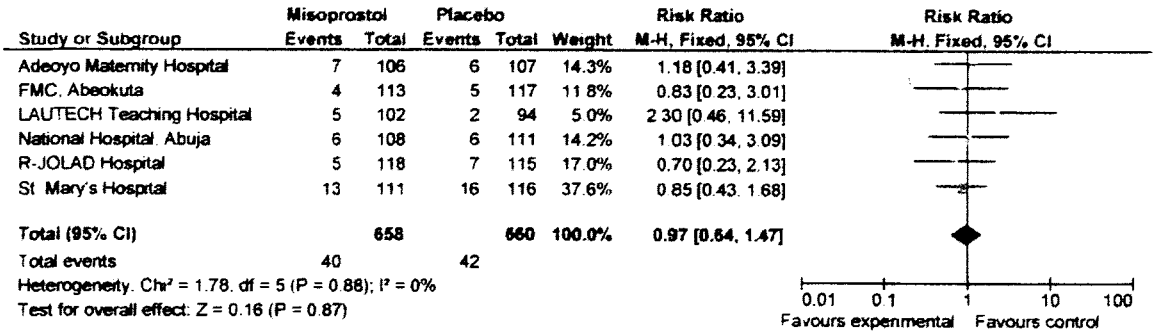

Fig. 6. Comparison of the primary outcome measure (blood loss of at least 500 mL) across study sites.

It has been proposed that misoprostol might augment the effect of oxytocin by producing sustained myometrial contraction [25]. According to this hypothesis, the early-onset myometrial contraction induced by parenteral oxytocin is further enhanced by the late-onset myometrial contraction produced by misoprostol. The synergistic effect of the 2 drugs potentially reduces the risk of further blood loss. If this proves to be true, misoprostol could be added to oxytocin both to prevent and to treat postpartum hemorrhage.

A major strength of the present multicenter study was the consistency of results across centers. Tests for heterogeneity revealed no variability in any of the study outcomes across the 6 sites, and the trend in each center was consistent with the overall findings. Another strength was the fact that active management of the third stage of labor was consistently practiced at all sites and always included administration of a uterotonic, even though the specific uterotonic used may have varied between centers. The effectiveness of the method used for measuring blood loss in the study has been established previously [10]. The trial sites included a mix of secondary and tertiary healthcare facilities, thus reflecting typical clinical practice settings.

Differences in the use of uterotonics among the participating institutions were a potential limitation of the present study. However, the pragmatic nature of the investigation enabled each study site to use the uterotonic routinely employed in active management of the third stage of labor.

The present data indicate that misoprostol in combination with a uterotonic for active management of the third stage of labor tends to prevent postpartum hemorrhage without serious adverse effects. The possibility of using misoprostol in this way has received limited attention; only 2 other studies were identified that have investigated this issue [14,15]. We recommend larger studies to evaluate further this potential before implementing policies that promote the widespread use of misoprostol in addition to a routine uterotonic.

Acknowledgments

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Conflict of interest

The authors have no conflicts of interest.

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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.

Background

Excessive bleeding from the genital tract after birth, or postpartum haemorrhage (PPH) is the major cause of maternal deaths in many low-income countries. The global estimate is 125,000 deaths per year [1]. In South Africa, 240 of 2,445 maternal deaths reported between 1999 and 2001 were due to postpartum haemorrhage, the third most common cause [2]. In a community-based study in Senegal, estimates of maternal mortality ratio in three regions ranged from 436 to 852 per 100,000 live births. Two-thirds were due to direct obstetric causes, the commonest being haemorrhage [3]. In the United Kingdom, the risk of maternal death from haemorrhage is about 1 in 100 000 births [4]. The potential to save mothers' lives with medical interventions for haemorrhage is thus considerable.

There is good evidence that a policy of active management of the third stage of labour [5], and one component of active management, the routine administration of uterotonics (drugs to contract the uerus) such as oxytocin [6] or oxytocin and ergometrine [7], are effective in reducing the risk of postpartum haemorrhage.

When postpartum haemorrhage occurs, a number of medical and surgical interventions are used to control the bleeding [8]. A crucial aspect of both prevention and treatment of postpartum haemorrhage is uterotonic therapy. The most commonly used agents are injectable oxytocin and/or ergometrine.

Misoprostol is a methyl ester (a synthetic analogue) of natural prostaglandin E1. It is marketed and registered for use in the prevention and treatment of peptic ulcer disease caused by prostanglandin synthetase inhibitors. Administered orally or sublingually, peak plasma concentrations of misoprostolic acid are achieved in less than 30 minutes [9]. It is a thermostable drug [9] and is relatively inexpensive.

Administered orally or vaginally, it is an effective agent for the induction of abortion [10] and of labour [11].

Misoprostol for routine prevention of postpartum haemorrhage

Oral and rectal misoprostol have been used for routine management of the third stage of labour (after the birth). Several small trials have given conflicting results. The main side-effects have been shivering and pyrexia, which are dose-dependent [12]. In the large WHO Collaborative Trial of Misoprostol in the Management of the Third Stage of Labour [13] and a systematic review of the topic [14], blood loss >1,000 ml and use of additional oxytocics (the primary outcomes in the WHO trial) were more frequent with misoprostol than with injectable oxytocics, indicating that injectable oxytocics should remain the drug of choice for routine prophylaxis. On the other hand, blood transfusion was used less frequently in the misoprostol group. This may have been a chance occurrence (it was not a primary outcome for the trial). Secondly, there could be a synergistic pharmacological effect between misoprostol and conventional uterotonics, which were given to most women with increased blood loss. Many women in the misoprostol group thus received misoprostol as well as conventional uterotonics, whereas those in the oxytocin group received only conventional oxytocics. Thirdly, we have suggested in the report of a pharmacokinetic study linked to the WHO trial that the longer time to peak levels of misoprostol (20–30 minutes) than syntocinon (3 minutes) may account for more early blood loss with misoprostol [15]. This does not exclude the possibility that misoprostol may have an effect on more persistent bleeding. Physiological studies have also shown a more rapid onset of uterine contractions following syntometrine than misoprostol after delivery [16].

Misoprostol has been widely recommended for the prevention of postpartum haemorrhage when other methods are not available [17].

Misoprostol for treatment of postpartum haemorrhage

Apart from the prophylactic use of misoprostol in the third stage of labour, the therapeutic use of misoprostol for the treatment of postpartum haemorrhage has been promoted on the basis of unblinded studies. In a systematic review [18] we located 6 uncontrolled reports (41 women) [19-24] and one small, unblinded randomised trial [25]. This method has entered clinical use, particularly in developing countries, without systematic research to document the optimal route and dosage, effectiveness or risks of this treatment. The urgent need for randomised trials of this new intervention has been emphasised [26]. If effective it could have a major impact on maternal mortality, particulary in under-resourced countries. If not, its use should be discouraged because of the dangers of side-effects, and the risks associated with widespread introduction of misoprostol into health systems in which it might be used for labour induction in inappropriate doses, with the risk of fetal compromise and uterine rupture [27,28].

Route and dosage of misoprostol

The most common regimens reported for the treatment of postpartum haemorrhage are 800 [23] or 1,000 μg [19,21] rectally. We reviewed the literature on the pharmacokinetics of misoprostol administered by various routes [18]. The oral route has the most rapid uptake, but the shortest duration. The rectal route has slow uptake but prolonged duration. The buccal or sublingual route has rapid uptake, prolonged duration and greatest total bioavailability. In order to improve the rapidity of onset of action and the

overall bioavailability, we modified the reported practice of using 1,000 μg rectally, by administering 200 μg orally, 400 μg sublingually and 400 μg rectally.

Objective

The objective of this study was to determine the side-effects and effectiveness of high-dose misoprostol for the treatment of postpartum haemorrhage by means of a double-blind, placebo-controlled, randomised clinical trial. The hypothesis was that measured blood loss of 500 ml or more in the hour after enrolment would be significantly less frequent in the misoprostol than in the placebo group.

Methods

The study was conducted at the East London Hospital Complex (Frere Maternity and Cecilia Makiwane Hospitals, Eastern Cape) and Tembisa and Chris Hani Baragwanath Hospitals, Gauteng, South Africa, between Jan 2002 and Dec 2003. All are busy referral hospitals.

Treatment packs were prepared independently, ordered in computer-generated random sequence and numbered consecutively. The packs contained either misoprostol 5 × 200 μg or inactive placebo.

The treatment sequence was kept sealed, and the code broken only after complete entry and checking of all trial data.

A confidential interim analysis, blind to which group was which, was performed by AMG after the first 100 enrolments. Evidence of clear benefit or harm for either group would have prompted stopping the trial, which was not the case.

Women in labour were given basic information about the trial in the form of notices in the labour rooms (Table 2 [see additional file 1]). Management of labour 3rd stage was routine active management with oxytocin 10 units or syntometrine one ampoule soon after the birth. Women aged 18 or more with bleeding judged by the clinician to be more than expected at least 10 minutes after delivery, and thought to be due to uterine atony and requiring additional uterotonic therapy, were given all the routine treatment for PPH (intravenous infusion, uterotonics, etc) from a special 'PPH Trolley' kept in the labour ward. The uterotonics used were oxytocin by intravenous infusion, and/or oxytocin/ergometrine, at the discretion of the attending clinician. Prostaglandin preparations such as sulprostone were not routinely available in the labour wards, and were not part of routine management of postpartum haemorrhage in the participating units.

Once all emergency treatment was instituted, and if the women were in a position to give fully informed consent, they were given detailed information about the trial and asked whether they wished to participate. Information about the trial was given verbally and in writing in English or Xhosa (Table 3 [see additional file 2]). Those who gave written consent were enrolled in the trial. Baseline data were documented. The next treatment pack containing either misoprostol 5 × 200 μg or inactive placebo was drawn and the number recorded. In addition to routine management, misoprostol or placebo (an inactive base) were given, 1 orally, 2 buccally/sublingually and 2 rectally, and the time recorded.

A low-profile plastic 'fracture bedpan' was placed under the woman's buttocks. In previous studies we have shown this to be an efficient method of collecting ongoing blood loss with very little spillage [29]. Any small swabs soaked with blood were dropped into the bedpan. After 1 hour, the blood collected in the bedpan was measured in a graduated measuring jug, the temperature was measured sublingually with a mercury thermometer, and any shivering was subjectively recorded as 'mild' (not causing any distress), 'moderate' or 'severe'.

All other management was by hospital staff according to the hospital routine for the management of postpartum haemorrhage.

After 24 hours, blood was collected for haemoglobin estimation and the hospital records checked for use of additional uterotonics and any other complications such as blood transfusion.

The primary outcome measures were specified prior to commencing the study: (1) measured blood loss ≥500 ml in 1 hour after enrolment; (2) mean measured blood loss in 1 hour after enrolment; (3) haemoglobin level day 1 after birth <6 g/dl or blood transfusion; (4) Side-effects (pyrexia 38.5 °C or more, moderate or severe shivering 1 hour after enrolment).

Secondary outcome measures were: (1) blood loss ≥1,000 ml in 1 hour after enrolment; (2) blood transfusion; (3) haemoglobin level 1 day after birth <8 g/dl or blood transfusion; (4) additional uterotonic given after enrolment; (5) manual removal of the placenta; (6) evacuation of retained products of conception; (7) hysterectomy; (8) maternal death.

Sample size calculation

In the WHO misoprostol trial control group (routine syntocinon), significant postpartum haemorrhage (blood loss >1000 ml) occurred in 2.8% of women. Of these 25% lost >1,500 ml. To reduce blood loss >500 ml after

enrolment from 25% to 10%, would require 112 per group (α = 95%, β = 80%).

Data were collected on a data form, entered onto an excel spreadsheet, checked for accuracy, then analysed using Epi-info 2002 (United States Department of Health and Human Services, Centres for Diseases Control and Prevention, Epidemiology Program Office) and Review Manager (RevMan) [Computer program] version 4.2 for Windows. Oxford, England: The Cochrane Collaboration, 2003. Results were expressed as relative risks or mean difference with 95% confidence intervals. Analysis was by intention to treat.

Ethical considerations

All women enrolled in the trial received all the conventional management available for postpartum haemorrhage, in addition to the trial medication (misoprostol or placebo). Rapid conventional therapy was facilitated by the ready availability of the 'PPH trolley' with all the necessary materials. This trolley was also available for women not enrolled in the trial. Participation was limited to women who were in a position to give fully informed consent. Ethical approval was given by the Committee for Research on Human Subjects, University of the Witwatersrand, and the Ethics Committee, East London Hospital Complex. The trial complied with the Helsinki Declaration for research on human subjects.

Results

Altogether 244 women were enrolled in the trial. The pack numbers for 6 women were incompletely filled in on the data sheets. The group allocation of these women was therefore unknown, and they could not be included in the analysis. Of these 6 women, the highest measured blood loss after enrolment was 220 ml; none had pyrexia >37.5°C, one had moderate shivering, one had a blood transfusion and none had day 1 haemoglobin level below 8 g/dl or other complications. There was no reason to expect that these exclusions occurred in any selective way which would introduce bias into the final samples, nor could their results have materially altered the conclusions of the study. All the remaining 238 women were included in the analyses.

The baseline characteristics are shown in table 1. As would be expected in a randomised trial, the groups were well matched. Parity was not recorded at all hospitals, but was similar between groups where recorded (misoprostol mean 1.61, SD 1.14; placebo 1.75, SD 1.26).

The outcomes are shown in table 1. In the placebo group, the primary outcome (measured blood loss within 1 hour after enrolment of 500 ml or more) was less frequent (9.2%) than the 25% prediction on which the sample size calculation was based. This may have been because the criteria for enrolment were loosely defined as 'more than expected blood loss', resulting in the enrolment of women with less severe blood loss than anticipated. The fact that enrolment was limited to women who were able to received detailed information about the study, may have caused selection of less severe cases. Although the intention was to enrol women who had not responded to conventional therapy, the time taken for counselling of the women and obtaining informed consent may have resulted in some women responding to the primary treatment, and therefore the low rate of ongoing blood loss in the placebo group. The study was thus underpowered to detect a statistically significant reduction in the primary outcome. With misoprostol there was a trend to reduced blood loss ≥500 ml in 1 hour after enrolment (6/117 vs 11/120, relative risk 0.56; 95% confidence interval 0.21 to 1.46).

Other proxy estimations of blood loss showed no significant differences between the groups. The well-known side-effects of misoprostol, pyrexia and shivering, were significantly more frequent in the misoprostol than the placebo group.

Serious morbidity or mortality occurred in 5 women, all from the misoprostol group. Two women who continued to bleed despite conservative therapy underwent abdominal hysterectomy and recovered well. There were 3 maternal deaths:

Case 1

A 22-year old woman with one previous pregnancy developed postpartum haemorrhage after vaginal delivery, managed with a 40-unit oxytocin infusion. She was enrolled and received the trial medication 85 minutes after delivery. Thereafter she received a second 40-unit oxytocin drip, oxytocin/ergometrine (5 units/0.5 mg) and intravenous cyclokapron. In the hour after randomisation, measured blood loss was 125 ml. Subsequently bleeding continued and a sub-total hysterectomy was performed. Coagulopathy developed, bleeding continued through an abdominal drain, and she died 2 days after delivery despite re-laparotomy and multiple blood product transfusions.

Case 2

A 32-year-old woman, para 2, gravida 4, delivered normally after labour was induced with misoprostol, 25 µg vaginally and 4 doses of 50 µg orally. Before enrolment she received oxytocin10 units, ergometrine 0.5 mg and a 20-unit oxytocin infusion. She was enrolled and received the trial medication 140 minutes after delivery. After enrolment she received a further 40-unit oxytocin infusion. Measured blood loss in the hour after enrolment was

Table 1: Comparison of outcomes between women who received misoprostol or placebo, expressed as proportions (percent) or mean values [standard deviation]. Differences are expressed as relative risks or mean differences, with 95% confidence intervals.

	Misoprostol (117)		Placebo (121)			
Baseline characteristics	n		n			
Age (years)	116	27.1 [6.0]	119	26.2 [6.2]		
Ergometrine before enrolment	106	36 (34%)	104	34 (33%)		
Oxytocin ≥20 U before enrolment	116	82 (71%)	117	78 (67%)		
Primary outcomes:					RR/ MD	95% Conf. interval
Blood loss ≥500 ml*	117	6 (5.1%)	120	11 (9.2%)	0.56	0.21 to 1.46
Mean blood loss* [SD] (ml)	117	168 [163]	120	176 [173]	-8	-51 to 35
24 hour Haemoglobin <6 g/dL or blood transfusion	110	20 (18.2%)	116	17 (14.7%)	1.24	0.69 to 2.24
Pyrexia at 1 hour ≥38, 5°C	114	11 (9.6%)	118	2 (1.7%)	5.69	1.29 to 25
Shivering at 1 hour ≥ moderate	116	63 (54%)	118	30 (25%)	2.14	1.50 to 3.04
Secondary outcomes:						
Blood loss ≥ 1,000 ml*	117	1 (0.85%)	120	0 (0%)		
Blood transfusion	115	19 (17%)	119	15 (13%)	1.31	0.70 to 2.45
24 hour haemoglobin <8 g/dL or blood transfusion	110	43 (39%)	116	37 (32%)	1.23	0.86 to 1.75
Additional uterotonic after enrolment	111	63 (57%)	112	63 (56%)	1.01	0.80 to 1.27
Manual removal of the placenta	117	1 (0.85%)	121	4 (3.3%)	0.26	0.03 to 2.28
Evacuation of retained products of conception	117	2 (1.7%)	121	0 (0%)		
Hysterectomy**	117	3 (2.6%)	121	0 (0%)		
Maternal death**	117	3 (2.6%)	121	0 (0%)		

RR = relative risk; MD = mean difference; Conf = confidence; SD = standard deviation *Measured, within 1 hour after enrolment ** One woman died after hysterectomy and is counted in both outcomes

380 ml. Bleeding continued and a blood transfusion was commenced. Six and a half hours after delivery she suffered a cardiac arrest and was resuscitated. Examination in theatre found the uterus to be empty and intact. The main source of bleeding appeared to be a torn cervix, which was sutured. At 7.5 hours after delivery she suffered a second cardiac arrest and could not be resuscitated. The estimated total blood loss was 3,000 ml.

Case 3

A woman with one previous delivery by caesarean section, developed postpartum haemorrhage of about 500 ml after a vaginal delivery. She was enrolled 85 minutes after delivery. Measured blood loss over the next hour was 425 ml, after which she developed hypotension and cardiorespiratory arrest. As no post-mortem examination was performed, the possibility of internal bleeding from a dehisced caesarean section scar could neither be confirmed nor excluded.

Unresponsive uterine atony was therefore not confirmed as the main cause of any of the deaths.

Discussion

Pyrexia and shivering were common side-effects of misoprostol, as found in previous studies. Three women, all in the misoprostol group, had severe pyrexia >40°C. Previous studies of high-dose misoprostol for the treatment of postpartum haemorrhage have mostly used the rectal route, and none has had sufficient numbers to be likely to detect rare adverse outcomes such as severe pyrexia. These side-effects may be related to the rapid absorption of misoprostol given orally, and the rapid absorption and high bioavailability when given sublingually. Because of these serious side-effects, we would recommend that for future trials the dose be reduced.

Several previous unblinded studies have reported dramatic effects of misoprostol when used to treat postpartum haemorrhage. In 6 observational studies [19-24], 41 women with postpartum haemorrhage were treated with misoprostol 1,000 μg rectally (32 women), 200 μg rectally (5 women), 200 μg orally 2-hourly (2 women) or 800 μg intrauterine (2 women). In all but 2 of the women (who received 1,000 μg rectally), a prompt response to the treatment was reported. In a single blind randomised trial [25] subjective prompt cessation of bleeding was reported in 30/32 women who received misoprostol 800 μg rectally

compared with only 21/32 who received oxytocin 5 units plus ergometrine 0.5 mg intramuscularly.

Conclusions

In our double blind trial we have been unable to confirm the dramatic effects of misoprostol reported previously in unblinded studies. Our results, however, are consistent with anything from a large beneficial effect to a smaller adverse effect (relative risk of additional blood loss of 500 ml or more anywhere between a reduction of 79% and an increase of 46% with misoprostol). It is important that this possible benefivial effect be assessed by sufficiently powered randomised trials before the treatment enters routine clinical use.

List of abbreviations

PPH: postpartum haemorrhage; SD: standard deviation

Competing interests

None known.

Authors' contributions

GJH prepared the first draft of the protocol and the final manuscript, and oversaw the clinical work

CN assisted with the design of the protocol and data collection sheet, initiated enrolment at two sites, supervised some of the data collection and contributed to the manuscript

SF, ZM, LM, MS and ZJ commented on the protocol, conducted the clinical procedures and collected data.

SF entered and collated the data

BM undertook the literature search and commented on the protocol.

GW contributed to the protocol development

AMG contributed to the protocol development and undertook the blinded interim analysis

All authors read and approved the final manuscript

Additional files

Additional file 1 - Table 2. Notice informing women about the trial, MS Word file: HofmeyrFile1.doc

Additional file 2- Table 3: Information and consent form. MS Word file: HofmeyrFile2.doc

Additional material

Additional File 1

Table 2. Notice informing women about the trial
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Additional File 2

Table 3: Information and consent form
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SHORT COMMUNICATION

Misoprostol in the treatment of postpartum haemorrhage in addition to routine management: a placebo randomised controlled trial

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Postpartum haemorrhage remains a leading cause of maternal mortality, despite treatment with conventional methods. In this randomised controlled trial, we compared misoprostol 600 μg (200 μg orally and 400 μg sublingually) with placebo in the treatment of postpartum haemorrhage in addition to routine treatment. One hundred and sixty consenting women who delivered vaginally with measured blood loss ≥500 mL and for whom inadequate uterine contraction was thought to be a possible factor were given either misoprostol or placebo in addition to normal treatment and after routine active management with uterotonics. Blood loss was measured by collection in a special plastic bedpan and side effects of treatment were recorded. Measured average additional blood loss was 325 mL (95% confidence interval [CI] 265 to 384 mL) with misoprostol and 410 mL (95% CI 323 to 498 mL) with placebo. No severe side effects were noted in the use of misoprostol.

Introduction

Haemorrhage is the largest single medical cause of maternal death, accounting for about 25% of the global total and claiming an estimated 150,000 lives annually.[1] Most of these deaths are due to postpartum haemorrhage, primarily due to atonic uterus. When postpartum haemorrhage occurs, a number of medical and surgical interventions are used to control bleeding.[2] One component in the treatment of postpartum haemorrhage is uterotonic therapy, most commonly with oxytocin and/or ergometrine. There is good evidence that their routine prophylactic use as part of the active management of the third stage of labour is effective in reducing the risk of postpartum haemorrhage.[3] Routine use of misoprostol for preventing postpartum haemorrhage has been found to be less effective than conventional uterotonics.[4]

Beyond preventive use of misoprostol, its therapeutic use for the treatment of postpartum haemorrhage has been promoted, particularly in resource-poor situations, where its non-parenteral administration, stability without refrigeration and low cost make it highly attractive. Unfortunately, misoprostol is beginning to enter clinical use without systematic research to document its optimal dosage, effectiveness or risks. In six 'uncontrolled' studies, 41 women with postpartum haemorrhage were treated with misoprostol using different doses and administration routes.[5] All but two of the women (who received 1000 μg misoprostol rectally) appeared to respond promptly to treatment. It is difficult to be sure whether these observed responses were due to misoprostol or other simultaneous treatments such as conventional uterotonics or bimanual compression of the uterus. A small randomised trial with 64 study subjects involving the use of misoprostol (800 μg) rectally showed promising results.[6]

The evidence for the effectiveness of misoprostol for treatment of postpartum haemorrhage is thus promising but unsubstantiated. A dose of 600 μg appears safe in the prevention of postpartum haemorrhage, with an acceptable level of side effects and good increase in uterine activity. Prior to this study, we recommended a misoprostol dosage of 600 μg (200 μg orally and 400 μg sublingually) for the management of postpartum haemorrhage based on available knowledge of pharmacokinetic, physiological and clinical studies of misoprostol (Hofmeyr, unpublished report for WHO). The combined route of oral and sublingual administration was used as these two routes combined together have shown the most optimum pharmacokinetic profile (rapid onset, highest peak and long duration).

The objective of this trial was to evaluate whether misoprostol administered 200 μg orally and 400 μg sublingually

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is safe and confers additional benefits when combined with conventional management for women with postpartum haemorrhage (measured blood loss ≥500 mL).

Methods

Women admitted to the labour room of the Farafenni APRC Hospital, Gambia were given information about the trial in an appropriate local language by a midwife and invited to sign or thumb print consent to participate.

Management of the third stage of labour was by routine active management with oxytocin 10 units or syntometrine one ampoule (5 mL). Women diagnosed with postpartum haemorrhage (measured blood loss ≥500 mL within 1 hour) and for whom inadequate uterine contraction was thought to be a possible factor, were given standard routine treatment for postpartum haemorrhage (rubbing the uterus if it was found to be poorly contracted, commencing an intravenous infusion, administrating oxytocics, delivering the placenta if undelivered and emptying the bladder).[7] In addition, they were enrolled by opening the next in a series of randomised treatment packs in opaque envelopes containing either misoprostol three 200 μg or placebo tablets, each administered as one tablet orally and two tablets sublingually. The tablets were similar in size and colour but not in shape. Efforts to obtain identical placebo tablets were unsuccessful. Although there was no account where the midwife caught sight of the tablet, this is not sufficient guarantee of adequate blinding.

Immediately after administration of the study medication, the woman was positioned on a clean bedpan on top of a fresh large perineal pad with plastic backing, for a further period of at least 1 hour. The hour was measured using a standard timer. However, the blood collection ended only when the midwife considered active bleeding to have stopped. The blood collected in the bedpan was then transferred to a measuring jar. The measuring jar and all gauzes and pads used were put in a standard plastic bag and the total difference between the dry and wet weights was calculated. A 100-g increase in weight was considered to be equivalent to 100 mL of blood (i.e. specific gravity of blood was assumed to be 1 g mL^{-1}). Under-estimation of blood loss was unavoidable as some blood can be expected to spatter on the drapes and on the gowns of the attendant although attempts were made to minimise such losses. Furthermore, maternal blood contained in placental interstices was also not measured. As these under-estimations, as well as any over-estimations (e.g. due to amniotic fluid) were likely to be distributed equally between the randomised study groups, there was no need for such corrections.

Side effects were recorded by the attending midwife as they were observed or reported in response to direct questioning. Haemoglobin level was estimated between 12 and 24 hours after delivery. Time of delivery and taking of the haemoglobin estimation were recorded on the data form. Haemoglobin was measured by taking a fingerprick and by using a Heamocue Haemoglobin machine and cuvette (HemoCue, Ängelholm, Sweden). Demographic and obstetric characteristics of the women were recorded to assess comparability of the study groups at trial entry and data were collected on outcomes and possible confounding factors.

Exclusion criteria were the lack of consent for participation, women who had a caesarean section, blood loss <500 mL in the first hour after delivery, if the delivery occurred at <28 weeks of gestation and if inadequate uterine contraction was not thought to be a possible causative factor for the postpartum haemorrhage. The primary outcome measure was average additional blood loss after enrolment. Secondary outcome measures were frequency and severity of side effects, assessed and recorded using standardised data capture sheets, additional blood loss ≥500 mL after enrolment, clinical complications (need for blood transfusion, hysterectomy) and haemoglobin 12–24 hours after delivery.

Sample size was calculated using the primary outcome measure. It was assumed that, to detect a 100-mL difference in additional average blood loss after enrolment (assuming mean additional blood loss of 400 mL in the placebo group and 300 mL in the misoprostol group, and a standard deviation of 200 mL in both groups) at 5% significance level with 80% power, 63 women per group would be required. Data were doubly entered, checked and cleaned using Epi-Info 6.0 and analysed using Stata 7.0 (Stata, Texas, USA). The randomisation code was broken only after entry and checking of data. Comparisons were by the χ^2 or Fisher's exact probability test and relative risks with 95% confidence intervals (95% CI) for categorical data, while for continuous data the *t* test was used and 95% confidence intervals were calculated. Ethics approval was obtained from the ethics committee of the Gambia Government and MRC Laboratories. An independent data monitor (Dr A. M. Gülmezoglu) reviewed the data collected from the initial 80 women and recommended that the study to continue until complete recruitment.

Table 1. Comparison of baseline variables between women allocated to receive misoprostol or placebo in the treatment of postpartum haemorrhage in addition to normal treatment. Values are shown as mean [SD] or *n* (%).

	Misoprostol (n = 79)	Placebo (n = 81)
Age (years)	24.6 [6.4]	24.1 [5.4]
Primiparous	23 (29.1)	26 (32.1)
Parity ≥ 6	12 (15.2)	12 (14.8)
Fundal height (weeks)	24.7 [3.6]	24.6 [2.9]
Twin delivery	8 (10.1)	5 (6.2)
Singleton stillbirth	9 (11.4)	13 (16.1)
Birthweight for singletons (g)	2891 [739]	2909 [692]
Blood loss prior to randomisation (mL)	702 [191]	757 [338]
Episiotomy/tear	18 (22.8)	16 (19.8)
Manual removal of placenta	3 (3.8)	3 (3.7)
Use of therapeutic uterotonics	22 (27.9)	28 (34.6)

Results

During the study period from November 2002 to October 2003 there were 1094 vaginal deliveries at Farafenni AFPRC hospital. In 1048 women (95.8%), consent was obtained and blood loss was measured, and in 174 of these women (16.6%) blood loss was measured to be ≥500 mL. In 160 women, inadequate uterine contractions were thought to be a possible causative factor for the postpartum haemorrhage.

There were no withdrawals after enrolment, and all outcomes were analysed according to the allocated study group. The two groups were similar with regard to baseline characteristics (Table 1). There was no difference between the two groups in the amount, route and type(s) of other uterotonics used as prophylactic management and in the initial treatment of the postpartum haemorrhage. There was no problem recorded with the sublingual administration and acceptability of study medication. The study outcome variables are summarised in Table 2. Measured average additional blood loss was 325 mL (95% CI 265 to 384 mL) after misoprostol and 410 mL (95% CI 323 to 498 mL) after placebo, while the medians were 231 and 277 mL, respectively. Shivering and mild fever (temperature ≥37.5°C) were more common in the misoprostol group. There were only two women with a temperature higher than 39°C, and none of the participants had a temperature above 40°C. There was no report of severe side effects or other adverse events in the misoprostol group. With regard to the other secondary outcomes, namely, additional blood loss ≥500 mL (16.5% *vs* 28.4%) and ≥1000 mL (2.5% *vs* 6.2%) after enrolment, and use of additional uterotonics treatment for postpartum haemorrhage (3.8% *vs* 6.2%) was lower in the misoprostol than in the placebo group but not statistically significant. There was no difference in low postpartum haemoglobin or the proportion of patients requiring a blood transfusion between the two groups.

Table 2. Comparison of outcome variables between women allocated to receive misoprostol or placebo in the treatment of postpartum haemorrhage in addition to normal treatment. Values are shown as mean [SD] or *n* (%).

	Misoprostol (n = 79)	Placebo (n = 81)	Effect size* (95% CI)
Primary outcome			
Average blood loss after taking study medication (mL)	325 [264]	410 [397]	−85 [−191 to +20.5]
Secondary outcomes			
Shivering	23 (29.1)	8 (9.9)	2.95 (1.40 to 6.19)
Nausea	3 (3.8)	5 (6.2)	0.62 (0.15 to 2.49)
Headache	7 (8.9)	11 (13.6)	0.65 (0.27 to 1.60)
Temperature ≥ 37.5°C	16 (20.3)	8 (9.9)	2.05 (0.93 to 4.52)
Blood loss ≥ 500 mL	13 (16.5)	23 (28.4)	0.58 (0.32 to 1.06)
Blood loss ≥ 1000 mL	2 (2.5)	5 (6.2)	0.41 (0.09 to 1.77)
Postpartum Hb < 6 g dL^{-1} or blood transfusion	12 (15.2)	12 (14.8)	1.02 (0.49 to 2.15)
Hysterectomy	0	2 (2.5)	-
Use of additional uterotonics	3	5 (6.2)	0.62 (0.17 to 2.25)

* Relative risk except for average blood loss after taking study medication for which the difference between means employed instead.

Discussion

The purpose of this trial was to explore any additional effect to conventional methods, and to establish the safety of 200 μg oral and 400 μg sublingual misoprostol in addition to routine uterotonics in the treatment of postpartum haemorrhage. Side effects were mild to moderate and comparable with findings from previous randomised controlled trials of misoprostol to prevent postpartum haemorrhage.[8] The results of this study showed that the average additional blood loss, additional blood loss ≥500 mL and ≥1000 mL after enrolment, and use of additional uterotonics were lower in the misoprostol group but did not reach statistical significance.

In the large WHO collaborative trial of misoprostol in the management of the third stage of labour,[4] blood loss ≥1000 mL and use of additional uterotonics (the primary outcomes in this trial) were more frequent with misoprostol than with oxytocin 10 units, indicating that oxytocin should remain the drug of choice for routine prophylaxis in those settings where it is possible to administer this drug. Given the advantages of misoprostol (stability at high temperature, oral administration, long shelf-life and low cost) and the fact that postpartum haemorrhage remains an important cause of maternal mortality especially in the developing world, it is important to assess the use of misoprostol in the treatment of postpartum haemorrhage.

In the WHO collaborative misoprostol prevention trial, blood transfusion was used less frequently in the misoprostol group. However, this was not a primary outcome for this study, and hence, it may have been a chance occurrence. There could be a synergistic pharmacological effect between misoprostol and conventional uterotonics. Many women in the misoprostol group thus received misoprostol as well as conventional uterotonics, whereas those in the oxytocin group received only conventional oxytocics. A pharmacokinetic study linked to the WHO trial reported that a longer time to peak level with misoprostol (20–30 minutes) compared with syntocinon (3 minutes) may account for more early blood loss with misoprostol. Physiological studies have also shown a more rapid onset of uterine contractions following syntometrine compared with misoprostol after delivery. This does not exclude the possibility that misoprostol may have an effect on more persistent bleeding.

In this study, the use of blood transfusion was more frequent and postpartum haemoglobin was lower in the misoprostol group compared with the placebo group. The

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seemingly positive results in the misoprostol group regarding additional blood loss and use of uterotonics should be interpreted cautiously as this is a small study with limited power to only detect large differences. Postpartum haemorrhage accounts for more maternal deaths in places where access to hospital delivery is limited and in situations where other interventions to treat bleeding are not available. To conduct a large-scale randomised trial of misoprostol for treatment of postpartum haemorrhage in a setting in which conventional uterotonics are not available poses logistical and ethical problems. If misoprostol is found to be effective over and above the effects of conventional treatment, it is a biologically reasonable assumption that it will be at least as effective or more so when conventional uterotonics are not available.

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

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Summary

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

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

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

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

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Introduction

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

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

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

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

Methods

Participants

All women delivering vaginally were eligible to participate in the study if they had clinically diagnosed post-partum haemorrhage that was suspected to be due to uterine atony, and they needed additional uterotonics. Participants were enrolled from hospitals in Argentina, Egypt, South Africa, Thailand, and Vietnam between July, 2005, and August, 2008. Women were not eligible for the trial if: delivery was by caesarean section; misoprostol could not be given sublingually; any severe allergic or bleeding disorders (eg, haemophilia) were recorded; temperature was higher than 38·5°C; the delivery was defined as a miscarriage according to local gestational age limits; or the placenta was not delivered.

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

Randomisation and masking

A computer-generated randomisation sequence was derived centrally by Gynuity Health Projects (New York, NY, USA), and was stratified by country. Within the strata women were individually allocated by block randomisation (varying blocks of six and eight) to receive 600 μg misoprostol sublingually (three tablets of 200 μg; GyMiso, HRA Pharma, Paris, France) or matching placebo; both groups received standard uterotonics. The standard utertonic was in most cases 10 IU oxytocin given intramuscularly or by slow intravenous injection. The use of uterine massage was not consistent. The randomisation code was not shown to any participating trial centre or member of the study team until the trial was closed.

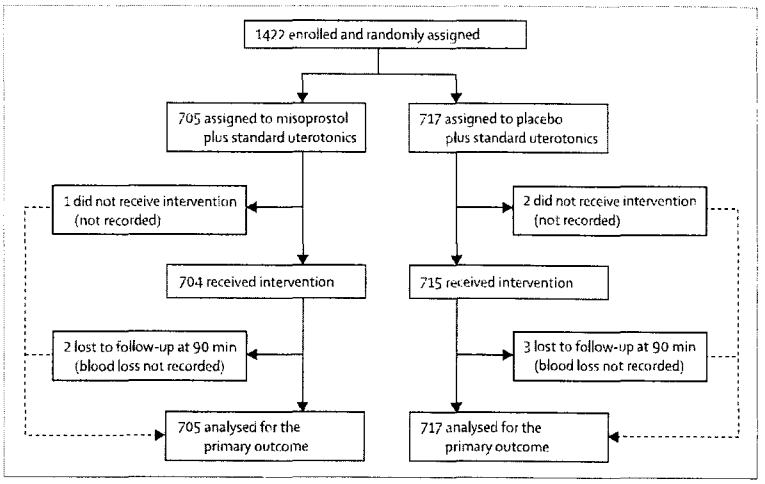

Figure 1: **Trial profile**

	Misoprostol (n=705)	Placebo (n=717)
Age (years)	26 (5·6)	26 (6·0)
Nulliparous	287 (41%)	290 (40%)
Type of uterotonic given during active management of third stage of labour		
Oxytocin	688 (98%)	701 (98%)
Ergometrine	44 (6%)	49 (7%)
Prostaglandins	8 (1%)	6 (1%)
Any uterotonic taken before study drug	645 (91%)	647 (90%)
Birthweight of neonate (g)	3148 (589)	3164 (557)

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

Table 1: **Baseline characteristics of participants**

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

Procedures

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

	Misoprostol (n=705)	Placebo (n=717)	Relative risk (95% CI)
Primary outcome			
Blood loss of ≥500 mL within 60 min after randomisation	100 (14%)	100 (14%)	1·02 (0·79 to 1·32)
Secondary outcomes			
Blood transfusion after randomisation	103 (15%)	117 (16%)	0·89 (0·70 to 1·14)
Haemoglobin concentration of <80 g/L within 24 h post partum or need for blood transfusion*	121 (18%)	139 (20%)	0·89 (0·72 to 1·11)
Blood loss after randomisation			
Within 60 min (mL)	200 (100–306)	200 (100–340)	0 (0 to 0)†
≥1000 mL	9 (1%)	9 (1%)	1·02 (0·41 to 2·55)
Within 90 min (mL)‡	250 (120–440)	250 (120–450)	0 (−40 to 20)†
≥500 mL	149 (21%)	162 (23%)	0·93 (0·77 to 1·14)
≥1000 mL	17 (2%)	22 (3%)	0·78 (0·42 to 1·47)
Any uterotonic after randomisation	188 (27%)	203 (28%)	0·94 (0·79 to 1·11)
Maternal death	2 (<1%)	0	NA
Severe morbidity§	8 (1%)	10 (1%)	0·81 (0·32 to 2·00)

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

Table 2: **Primary and secondary outcomes**

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

The trial adhered to the methods used for blood loss measurement in the WHO trial of misoprostol for the prevention of post-partum haemorrhage.[4] Blood collection started immediately after the study drug was given. A fresh, non-absorbent sheet was placed under the buttocks of the woman. A low-profile plastic fracture bedpan was positioned below the woman's perineum to collect all subsequent blood lost for 90 min. The blood in the bedpan plus any spilled blood from the non-absorbent sheet or blood-soaked gauze swabs, or both, was transferred to a jar and the volume was measured. At the centre in Egypt, blood was collected into a calibrated plastic sheet that was placed below the woman immediately after she took the study drug, and the volume was measured accordingly. Measures of blood loss were recorded at 60 min and 90 min after randomisation. If bleeding did not stop, providers continued to provide standard care for post-partum haemorrhage according to local protocol. Thus the only addition to routine care was use of the study drug.

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

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

Statistical analysis

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

All analyses were by intention to treat. Comparisons between treatment groups for baseline characteristics were done to ensure comparability between study groups and to identify any possible confounding factors. Categorical outcomes are presented as percentages and were compared between treatment groups with relative risks (95% CI). Continuous outcomes were not distributed normally, so these data are presented as median (IQR) values; treatment groups were compared from the difference in median values, and 95% CIs were derived with a bootstrap procedure. Stratified analyses were done with the Cochran-Mantel-Haenszel statistic. Homogeneity tests (Breslow-Day) were done to assess the association between outcomes and treatment across participating countries. The number needed to harm (95% CI) was calculated for side-effects if a significant difference was recorded. All statistical analyses were done with SAS (version 9.2), and we judged p values of less than 0·05 to be significant.

This study is registered, number ISRCTN34455240.

Role of the funding source

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

Results

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

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

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

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

	Misoprostol (n=704)*	Placebo (n=717)	Relative risk (95% CI)	Number needed to harm (95% CI)†
Within 60 min after randomisation				
Shivering				
Any	455 (65%)	230 (32%)	2·01 (1·79–2·27)	3·1 (2·7–3·6)
Severe	80 (11%)	7 (1%)	11·64 (5·41–25·03)	9·6 (7·8–12·6)
Temperature				
≥38°C	303 (43%)	107 (15%)	2·88 (2·37–2·50)	3·6 (3·1–4·2)
≥40°C	18 (3%)	3 (<1%)	6·11 (1·81–20·65)	46·7 (29·4–113·6)
Diarrhoea				
Any	2 (<1%)	3 (<1%)	0·68 (0·11–4·05)	..
Severe	0	0	NA	NA
Vomiting				
Any	36 (5%)	16 (2%)	2·30 (1·28–4·09)	34·7 (20·7–107·5)
Severe	2 (<1%)	2 (<1%)	1·02 (0·14–7·21)	..
Nausea				
Any	45 (6%)	35 (5%)	1·31 (0·85–2·01)	..
Severe	2 (<1%)	1 (<1%)	2·04 (0·18–22·41)	..
Within 90 min after randomisation				
Shivering				
Any	514 (73%)	252 (35%)	2·08 (1·86–2·32)	2·6 (2·3–3·0)
Severe	95 (13%)	13 (2%)	7·44 (4·21–13·16)	8·6 (6·9–11·1)
Temperature‡				
≥38°C	406 (58%)	137 (19%)	3·00 (2·55–3·53)	2·6 (2·3–3·0)
≥40°C	48 (7%)	3 (<1%)	16·21 (5·07–51·78)	15·6 (11·6–22·3)
Diarrhoea				
Any	6 (1%)	5 (1%)	1·22 (0·37–3·99)	..
Severe	0	0	NA	NA
Vomiting				
Any	45 (6%)	25 (3%)	1·83 (1·14–2·96)	34·4 (19·6–153·8)
Severe	2 (<1%)	2 (<1%)	1·02 (0·14–7·21)	..
Nausea				
Any	60 (9%)	49 (7%)	1·25 (0·87–1·79)	..
Severe	2 (<1%)	1 (<1%)	2·04 (0·18–22·41)	..

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

Table 3: **Side-effects**

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

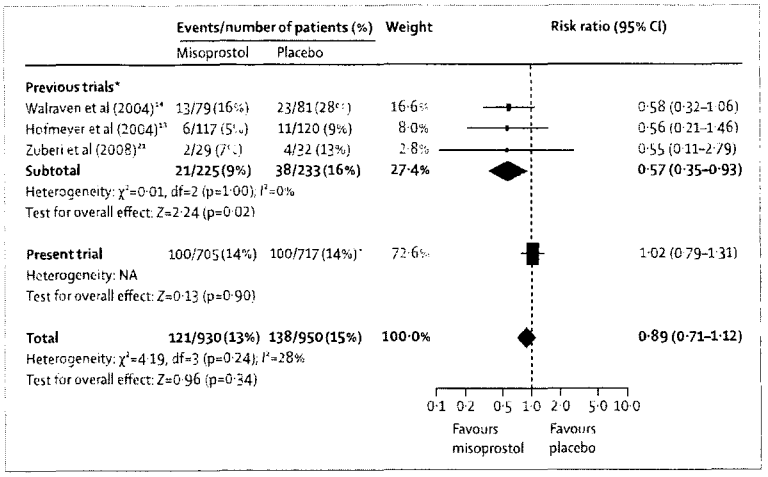

Figure 2: **Meta-analysis of blood loss of 500 mL or more within 60 min after randomisation in trials of misoprostol as an adjunct to standard uterotonics for treatment of post-partum haemorrhage**
NA=not applicable. *Misoprostol doses were: 400 μg sublingually and 200 μg orally;[14] 400 μg sublingually,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

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

Discussion

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

Three randomised trials have studied use of misoprostol plus uterotonics versus uterotonics alone for treatment of post-partum haemorrhage: two were published before our study was planned,[13,14] and one was published while our trial was underway.[21] Meta-analysis of these three trials found a reduction of 40–50% in blood loss of 500 mL of more in women on misoprostol versus those on placebo (figure 2). The dose and route of administration of misoprostol differed between the three trials, but these differences are unlikely to account for variations in outcome. Variations could possibly be the result of chance since the studies have small sample sizes, and could be compounded by publication bias from other small trials with less optimistic results that have not been published.[22] In total, the three trials enrolled 458 women, whereas a major strength of our study is the large sample size (1422 women from five countries) and statistical power. Meta-analysis of the three previous trials and our trial shows a pooled risk ratio of 0·89 for blood loss with misoprostol versus placebo (figure 2). These results underscore the importance of adequately powered large trials since the pooled results of several small trials can suggest a promising beneficial effect that is not necessarily real.

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

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

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

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

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

Contributors

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

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Conflicts of interest

We declare that we have no conflicts of interest.

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29.

Umbilical vessel oxytocin administration for retained placenta: In vitro study of various infusion techniques

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OBJECTIVE: The aim of our study was to investigate whether the discrepancies in results between various studies of umbilical vein administration of oxytocin for retained placenta may be related to differences in the infusion techniques used.
STUDY DESIGN: An in vitro, descriptive study was performed. Contrast medium was injected into the umbilical vessels of 25 freshly delivered placentas and sequential x-ray films were taken.
RESULTS: Capillary filling was inconsistent after injection of 20 ml of solution into the umbilical vein without or with "milking" of the cord (1/5 and 2/5, respectively). These are the techniques most commonly used in reported controlled clinical studies. Injection via an infant mucus aspiration catheter introduced along the umbilical vein to 5 cm from the placental insertion demonstrated a cotyledonary pattern in three of five cases after 20 ml and in all 5 after 30 ml.
CONCLUSION: The latter method (use of increased infusion volumes) is recommended in future studies to determine the effectiveness of umbilical vein administration of oxytocin for retained placenta. (Am J Obstet Gynecol 1993;168:793-5.)

Key words: Retained placenta, third-stage labor, umbilical vein, placentography, in vitro study

Retained placenta is a serious complication of childbirth. The injection of oxytocin into the umbilical vein has been suggested as a simple and safe method of treatment. If such treatment were shown to be effective, it would be of major benefit to women worldwide.[1]

Considerable disagreement exists in the literature concerning the effectiveness of umbilical vein administration of oxytocin for retained placenta. Six rather small randomized control trials (numbers ranging from 30 to 60) have recently been reviewed by Carroli.[1] The incidence of manual removal of the placenta was increased in two studies and reduced in four studies, the typical odds ratio for all the studies being 0.50 (95% confidence interval 0.30 to 0.83). A more recent study involving 220 women, 20 of whom were excluded from analysis, showed no reduction in the incidence of manual removal of the placenta.[2]

The volume, concentration, and route of oxytocin administered in these studies appears to have been chosen empirically. In the majority 10 IU of oxytocin in 20 ml of saline solution has been used, presumably because 20 ml syringes are readily available, with or without "milking" of the cord after injection. In one small study that showed the greatest benefit,[3] 100 IU in 30 ml was used, and in one of the negative studies[4] 10 IU in 10 ml was used. Differences in technique may account for some of the discrepancies in reported results.

The purpose of this study was to determine the most efficient method of delivering infused fluid to the placental capillary vasculature.

Material and methods

Freshly delivered placentas were immersed in saline solution at 37° C and studied within 30 minutes of delivery in most cases. The cord was clamped 30 cm from the insertion to the placenta. Sodium iothalamate 20 gm/100 ml (Infuso-Conray, Maybaker) was injected in aliquots of 5, 5, 10, and 10 ml, and x-ray films of the placenta were obtained after each injection (Fig. 1). The whole procedure took between 5 and 10 minutes in each case. The following methods were used for injection:

1. Injection was carried out via an infant mucus-aspiration catheter introduced along the umbilical vein to 5 cm from the placental insertion of the cord. The cord was occluded with finger pressure around the catheter during injection.
2. Injection was carried out after the cord was allowed to bleed freely; it was then reclamped and

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Fig. 1. Placental radiograph after injection of 30 ml of contrast medium via an infant mucus-extraction catheter introduced along the umbilical vein. It shows: *1*, catheter in umbilical vein; *2* through *5*, first-, second-, third-, and fourth-order branches, respectively; *6*, capillaries; *7*, cotyledon.

an 18-gauge intravenous cannula was introduced into the umbilical vein about 30 cm from the placenta.

3. Injection was carried out as in technique 2, without the cord initially being allowed to bleed.
4. Injection was carried out as in technique 3 but with "milking" of the fluid up the cord from a position 30 to 10 cm from the placental insertion, after injection of 20 ml.
5. Injection was performed into one umbilical artery near the insertion of the cord into the placenta, with an 18-gauge intravenous cannula.

The x-ray plates were examined after the technique used in each case was blinded, and the extent of the vascular perfusion by dye was recorded.

Results

Techniques 2 and 5 were found to be technically somewhat difficult, whereas techniques 1, 3 and 4 were straightforward. Insertion of the mucus-aspiration catheter as far as it would go resulted in the tube passing into a placental division of the umbilical vein for about one third of the placental diameter.

Table I shows that 20 ml was usually and 30 ml was always adequate to demonstrate placental capillaries with techniques 1 and 2 and to produce a cotyledonary pattern with technique 1. With technique 3, capillaries were demonstrated in only one case after injection of 20 ml.

The arterial injections cannot be compared directly with the venous techniques because injection was performed at a site close to the placenta, which would not be accessible in the clinical situation of a retained placenta. Cannulation of the artery further away from the placenta was difficult. As expected, only half the placenta was demonstrated. After filling the capillaries, the dye in three cases appeared to enter venous "lakes" rather than produce a cotyledonary pattern.

Comment

The reported clinical use of umbilical injection of oxytocin appears to have been empirically based. We are not aware of any studies to investigate possible mechanisms of action. The most likely mechanism would be a direct action on the myometrium underlying the unseparated placenta. It seems reasonable to assume that injected oxytocic agents would need to reach at least the villous capillary level to be able to diffuse across to the maternal circulation to cause myometrial contraction. The technique most commonly used in published reports, the injection of 20 ml of solution into the umbilical vein without previous bleeding, resulted in capillary demonstration in only one of five cases in this study (technique 3) and in two of five when the cord was "milked" after injection of 20 ml (technique 4). The inconsistency of this method, together with differences in exact technique, may well account for the differing results from various studies.

Injection into the umbilical artery (technique 5) is technically more difficult and on basic principles would seem not advisable because only half the placental surface would be reached. Injection into the umbilical vein after the cord was allowed to bleed (technique 2) produced consistent capillary filling but not a cotyledonary pattern with 30 ml, and it was technically somewhat difficult to introduce the needle into the collapsed vein.

The introduction of an infant mucus-extraction catheter into the cut end of the umbilical vein (technique 1) was technically easy and effective in producing capillary filling, as well as a cotyledonary pattern, when 30 ml was used. This technique can also be easily used when the cord has broken or torn but is still accessible and the vein has collapsed.

We are not aware of any clinical studies in which the latter technique has been used. On the basis of this study we would recommend the following technique to ensure that infused oxytocin reaches at least the placental capillary bed:

30.

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Measuring postpartum uterine contractions during the third stage of labour: a pilot study, using a novel minimally invasive technique

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ABSTRACT

Objectives: To determine the feasibility of measuring intra-uterine pressure prior to placental delivery, using a novel minimally invasive method. Design: A prospective exploratory physiological study. Methods: Thirty-six low risk women undergoing normal vaginal delivery were randomly allocated to four groups. Group A received 600 mcg rectal misoprostol; group B received 600 mcg oral misoprostol; group C received 10 international units oxytocin intramuscularly after delivery of the anterior shoulder; group D received intramuscular oxytocin, 30 minutes after delivery of the baby. A calibrated catheter-tip intrauterine pressure transducer was used to measure the intrauterine pressure. This was introduced into the placenta via the umbilical vein, and recorded on a standard tocograph. Results: It was technically easy to introduce the catheter through the umbilical vessels in all mothers. On assessment of the tocograms, it was possible to interpret 95 out of 108 recordings (88%). Conclusions: This study demonstrated the simplicity of a novel, minimally invasive method of measuring the duration and frequency of postpartum uterine contractions prior to delivery of the placenta.

Keywords: Postpartum Haemorrhage; Intrauterine Contractions

1. INTRODUCTION

Excessive maternal blood loss after childbirth is a leading cause of morbidity and mortality, particularly in births without skilled attendance and where injectable uterotonics are not readily available. In the prevention and management of postpartum hemorrhage, different uterotonics have been used. Apart from clinical trials, there is a need to describe the physiological effectiveness of uterine contractions, especially when new uterotonic agents are being investigated. The method used to date for in vivo measurements has been direct placement of a transducer into the uterine cavity [1]. This is an invasive procedure with the possibility of introducing infection from the lower genital tract into the uterus. In addition, because the catheter tip is not in a fluid medium, the accuracy of the measurements may be in doubt. Previous physiological study found some correlation between blood loss and uterine activity in women given intravenous oxytocin, intramuscular oxytocin-ergometrine, or oral misoprostol. Intrauterine pressure was measured with a pressure catheter inserted into the uterine cavity after delivery of the placenta [1,2].

We looked into the possibility of measuring uterine activity with various commonly used uterotonics viz: early and late oxytocin administration, and orally and rectally administered misoprostol. We are not aware of any previous studies measuring the uterine response to uterotonics administration prior to placental delivery, nor use of the umbilical vein for access to the intrauterine space. The measurement of uterine activity prior to placental delivery is relevant because of the recent completion of a large World Health Organization trial (>23 000 women receiving routine uterotonics), comparing controlled cord traction with allowing spontaneous delivery of the placenta (unpublished data).

The study objectives were to evaluate a novel, minimally invasive method of measuring intrauterine pressure prior to placental delivery; and to determine the uterine contraction pattern (duration and frequency) following administration of misoprostol and oxytocin.

2. WOMEN AND METHODS

The study protocol was approved by the Committee for Human Research of the University of the Witwatersrand, Johannesburg South Africa. Thirty-six low risk women who were to deliver at a tertiary hospital setting in Johannesburg, South Africa were recruited and gave informed consent. They were randomly allocated during the third stage of labor to four groups using a computer generated random sequence, in sequentially labeled treatment packs.

GROUP A 600 mcg rectal misoprostol as the active uterotonic agent.

GROUP B. 600 mcg oral misoprostol as the active agent.

GROUP C. 10 International Units oxytocin intramuscularly on delivery of the anterior shoulder. .

GROUP D. 10 International Units oxytocin 30 minutes after delivery.

A Hewlett Packard cardiotocogram monitor was activated to run the paper strip at 3 cm per minute. The tocogram pressure was zeroed after connection of a transducer tipped pressure catheter. Calibration was effected at 0 cm and 60 cm of water by immersion of the transducer in a 60 cm sterile water column. The time of delivery of the baby was noted. At delivery, with the placenta in situ, the pressure tip catheter was fed through the umbilical vein into the placental circulation and a soft clamp used to hold the catheter in place in the umbilical cord and prevent blood loss from the placental vasculature. The tocogram recording continued until either the placenta was spontaneously expelled or 30 minutes after insertion of the catheter.

The next in the sequence of refrigerated opaque envelopes containing the various randomized medications was opened to administer the contents, early or delayed oxytocin, and rectal or oral misoprostol. Oxytocin or ergometrine was to have been administered at any stage of the study if excessive uterine bleeding had occurred.

3. RESULTS

It was technically easy to insert the catheter through the umbilical vein in all mothers.

The baseline variables in terms of age and parity, for all the four groups of interventions, were similar (**Table 1**).

There was no difference between the various drugs in the three intervals of recordings as regards assessment for duration and/or frequency of uterine contractions. (**Table 2**)

In one woman, the placenta was delivered before the 30 minutes of recording time in the delayed oxytocin group, and one in the early oxytocin group. A few uninterpretable recordings on the tocogram were found in all groups recordings, and are represented by variations in 'n' in **Table 2**.

In the first 10 minutes of recording, 97% of tocograms, using the various oxytocics regimen, had interpretable frequency and or duration of uterine contractions. The rates were 83% in the second and the last 10 minutes.

4. DISCUSSION

We have described an innovative method for physiological study of intrauterine pressure with the placenta in situ, with the catheter transducer introduced via the umbilical vein. The advantage of this approach may be a reduction in risk of introducing infections from the lower genital tracts into the raw, postpartum endometrium, and the inconvenience to the mother of direct intrauterine catheter placement. The procedure is simple and reproducible, as shown in the outcome for the different uterotonics used, in this exploratory trial.

5. CONCLUSIONS

This pilot study demonstrated the ease of a novel, minimally invasive method of postpartum intrauterine pressure measurement prior to delivery of the placenta. The benefits of introducing the pressure catheter within the umbilical vein were to avoid the discomfort and possible

Table 1. Baseline data expressed as median and range.

	Oral Misoprostol		Rectal Misoprostol		Earily Oxytocin		Late Oxytocin		P value
	N	Median (rang)	N	Median (rang)	N	Median (rang)	N	Median (rang)	
Age	9	23 (18 - 37)	9	23 (18 - 37)	9	23 (18 - 43)	9	27 (18 - 32)	0.400
Parity	9	1 (1 - 6)	9	1 (1 - 2)	8*	1.5 (1 - 40)	9	2 (1 - 4)	0.258

*Missing data.

Table 2. Interpretable tocogram of frequency and duration of contractions, using different oxytocic regimens during different time intervals post delivery.

Frequency and/or duration of contraction	Oral Misoprostol, n = 9		Rectal Misoprostol, n = 9		Early Oxytocin, n = 9		Late Oxytocin, n = 9		Total	
	n	%	N	%	N	%	n	%	n	%
First 10 minutes	9	100	9	100	8	88.9	9	100	35/36	97
Second 10 minutes	7	77.8	9	100	7	77.8	7	77.8	30/36	83
Third 10 minutes	7	77.8	8	88.9	8	88.9	7	77.8	30/36	83

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introduction of infection associated with direct placement of a pressure catheter into the uterine cavity.

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Effect of sublingual misoprostol on severe postpartum haemorrhage in a primary health centre in Guinea-Bissau: randomised double blind clinical trial

Misoprostol in the third stage of labour and maternal mortality: a review

4 January 2006

Misoprostol in the third stage of labour and maternal mortality: a review (C. Justus Hofmeyr and A. Metin Gülmezoglu)

Introduction

We followed the responses following the paper by Høj et al with interest. Misoprostol has strong uterotonic and known pharmacologic effects on several organ systems. Pharmacologic effects other than on the uterus might explain certain inconsistencies such as the observation that misoprostol labour induction is associated with an increased risk of postpartum haemorrhage(1). Pharmacologic effects include inhibition of platelet-activating factor, gastrointestinal protection against nonsteroidal drug effects, irradiation injury, experimental gastric cancer, enteropathy and constipation, inhibition of leukocyte adherence and modulation of adhesion molecule expression, improved nutrient absorption in cystic fibrosis, reduced cholesterol and severity of peripheral vascular diseases, prolonged survival of cardiac and kidney transplantation, cyclosporine synergy, effectiveness in acetaminophen and ethanol hepatotoxicity, hepatitis and fibrosis, drug-induced renal damage, interstitial cystitis, lupus nephritis, hepatorenal syndrome, periodontal disease and dental repair, enhanced glycosaminoglycan synthesis in cartilage after injury, prevention of ultraviolet-induced cataracts, reduced intraocular pressure in glaucoma and ocular hypertension, synergism with the anti-inflammatory and analgesic effects of diclofenac or colchicines, reduced chemotherapy-induced hair loss, reduced recovery time from burn injury, and effectiveness in treating sepsis, multiple sclerosis and pancreatitis (2).

It is plausible that a drug with ubiquitous pharmacologic effects might have unexpected adverse effects when used in the third stage of labour. For the above reasons, we reviewed maternal mortality in randomised trials of misoprostol used in the third stage of labour.

We searched The Cochrane Controlled Trials Register and the electronic data base Pubmed/Medline were searched on the word misoprostol in December 2005 for randomised comparisons of misoprostol used for the prevention or treatment of postpartum haemorrhage with placebo or alternative methods (usually injectable uterotonics).

We identified 32 prevention and three treatment trials of postpartum haemorrhage where misoprostol was used as one of the interventions. Of the 32 prevention trials 24 made no reference to maternal deaths. While it is unlikely that maternal deaths would not have been reported had they occurred, we have included only those trials in which the presence or absence of maternal deaths was explicit, or has been confirmed by communication with trial authors in the meta-analysis. Differences were expressed as relative risks with 95% confidence intervals.

Results

Of 10 deaths reported in 11 trials (23 893 women), 8 occurred in women receiving misoprostol (relative risk 2.71, 95% confidence interval 0.80 to 9.21). In 24 trials no mention of maternal deaths was made.

Discussion

The primary motivation for the use of misoprostol in the third stage of labour is to reduce maternal mortality. Because mortality is such a rare outcome, no trials to date have been designed to assess the effect on mortality. However, the occurrence of several deaths in trials in women receiving misoprostol has raised concern.

The limitations of this quick review must be emphasised. Firstly, the numbers are small with wide confidence limits, and are consistent, at the 95% confidence level, with anything between a modest reduction and a large increase in maternal mortality with misoprostol. Secondly, this was a post-hoc analysis in response to an observed clustering of maternal deaths, and the statistical calculations need to be interpreted with circumspection.

These results should not be construed as evidence of an adverse effect of misoprostol on maternal mortality. On the basis of the results we propose, for further investigation, the hypothesis that misoprostol may have an as yet unexplained adverse effect on maternal homeostatic functions in the third stage of labour.

Conclusions

Because of the enormous potential benefits of an effective, orally active third stage uterotonic, and the likelihood that misoprostol will be used on a large scale worldwide, further research is essential to measure the possible beneficial and harmful effects of misoprostol more accurately. Enthusiasm for the use of misoprostol should not detract from international efforts to ensure access to all childbearing women to established, effective and safe uterotonics such as oxytocin.

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SYSTEMATIC REVIEW

Misoprostol to treat postpartum haemorrhage: a systematic review

Introduction

Postpartum haemorrhage (PPH) is a major cause of maternal mortality in low-income countries. Rates of 40 maternal deaths per 100,000 births in parts of sub-Saharan Africa[1] compare unfavourably with about 1 in 100,000 births in the United Kingdom. The potential to save mothers' lives with medical interventions for haemorrhage is thus considerable.

A crucial aspect of both prevention and treatment of PPH is uterotonic therapy. The most commonly used agents are injectable oxytocin and/or ergometrine. Misoprostol is a methyl ester (a synthetic analogue) of natural prostaglandin E_1 additionally methylated at C16. It is well absorbed from the stomach, appearing in the circulation within 90 seconds, and undergoes rapid de-esterification to its biologically active metabolite, misoprostolic acid (MPA). It is thermostable and is relatively inexpensive.

Systematic review[2] of the prophylactic use of oral misoprostol for the management of the third stage of labour found that misoprostol 600 μg was less effective than conventional uterotonics with respect to blood loss of 1000 mL or more (seven trials, 22,749 women, relative risk [RR] 1.3, 95% confidence interval [CI] 1.2 to 1.5). Shivering and pyrexia were common side effects.

The therapeutic use of misoprostol for the *treatment* of PPH has entered clinical use, particularly in developing countries, without systematic research to document the effectiveness, optimal dosage or risks of this treatment.

The aim of this review was to determine the route of administration and dosage of misoprostol most likely to be effective in the treatment of PPH and identify randomised controlled trials that compared misoprostol with any appropriate control groups.

Methods

Optimal route and dosage

Evidence was sought from the following: pharmacokinetic studies in pregnant and non-pregnant women; physiological studies in pregnant women; and randomised clinical trials comparing different routes but the same dosage of misoprostol which included an outcome reflecting the effect of misoprostol on pregnant uterine contractility. The data from pharmacokinetic and physiological studies were tabulated and analysed semi-quantitatively and qualitatively.

Systematic review of randomised controlled trials of misoprostol for the treatment of PPH

The criteria for considering studies for this part of the review were that they be randomised controlled trials. The types of participants were women assessed to have PPH (as defined by the trial authors). Pre-specified primary outcome measures were: blood loss >500 mL after enrolment; haemoglobin level 12–24 hours after enrolment <6 g/dL or blood transfusion; and maternal death or severe morbidity (laparotomy, hysterectomy, intensive care unit admission or organ failure).

The Cochrane Controlled Trials Register and the electronic database Pubmed/Medline were searched on the word 'misoprostol'. The date of the last search was September 2004. Researchers known to be active in the field were contacted for additional information. There were no language limitations.

All randomised and quasi-randomised controlled trials were included in the initial evaluation. Trials under consideration were evaluated for methodological quality and appropriateness for inclusion, without consideration of their results, independently by two reviewers (GJH and ZA). Data were extracted independently by the same two reviewers. Studies were combined using relative risks as the measure of effect size for binary outcomes. Weighted mean differences were used for continuous outcome measures. Fixed-effects meta-analysis was used for combination of studies if the trials were sufficiently similar in their design and interventions that a fixed-effects summary would be meaningful.

Results

Optimal route and dosage

Pharmacokinetic studies

Zieman *et al.*[3] randomised 10 pregnant women undergoing first trimester abortions and 10 non-pregnant women to oral or vaginal administration of misoprostol 400 μg (Table 1). Danielsson *et al.*[4] studied plasma misoprostol levels after administration of 200 μg (six women, data not

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Table 1. Serum misoprostol values and time course expressed as mean (standard deviation) following misoprostol administration by various routes.

Author	Dose (*n*)	Route of administration			
		Oral	Sublingual	Rectal	Vaginal
Time to peak concentration (minutes)					
Zieman *et al.*[3]	400 μg (20)	34 (17)			80 (27)
Danielsson *et al.*[4]	400 μg (12)	30			60–120
Tang *et al.*[5]	400 μg (40)	28 (15)	26 (12)		'longer'
Abdel-Aleem *et al.*[6]	600 μg (20)	20			
Khan and El-Refaey[7]	600 μg (20)	18 (8.8)		41 (16)	
Peak concentration (pg/mL)					
Zieman *et al.*[3]	400 μg (20)	227 (124)			165 (86)
Danielsson *et al.*[4]	400 μg (12)	±280*			±65*
Tang *et al.*[5]	400 μg (40)	288 (144)	575 (251)		125 (54)
Abdel-Aleem *et al.*[6]	600 μg (20)	345 (269)			
Khan and El-Refaey[7]	600 μg (20)	328 (103)		184 (65)	
Andolina *et al.*[8]	400 μg (10)	381			
Area under curve to 4 hours (pg/hours/mL)					
Zieman *et al.*[3]	400 μg (20)	273 (110)	503 (297)		
Khan and El-Refaey[7]	600 μg (20)	190 (125)		311 (141)	
Area under curve to 6 hours (pg/hours/mL)					
Zieman *et al.*[3]	400 μg (20)	300 (103)**			957 (542)**
Tang *et al.*[5]	400 μg (40)	403 (152)	744 (291)		434 (183)

* Estimated from published graph.
** 10 non-pregnant women only.

included in Table 1) or 400 μg misoprostol (12 women) orally or vaginally in the first trimester of pregnancy. Tang *et al.*[5] compared the pharmacokinetic parameters of four different routes: sublingual, oral, vaginal and vaginal with addition of water (data not included) in 40 pregnant women undergoing suction termination of pregnancy. Abdel-Aleem *et al.*[6] measured serum and colostrum misoprostol acid levels after misoprostol 600 μg orally in the postpartum period. Misoprostol acid appeared in the serum at 2 minutes (92 pg/mL) and reached peak levels after 20 minutes (345 [269] pg/mL), falling to low levels by 2 hours (28 [15] pg/mL). Misoprostol appeared in the colostrum in small amounts (21 [13] pg/mL). Khan and El-Refaey[7] randomised 20 postpartum women to rectal or oral administration of misoprostol 600 μg. Andolina *et al.*[8] studied 20 postpartum women given 400 μg postpartum as tablet or crushed in methylcellulose capsules (capsule data not included).

The data tabulated in Table 2 suggest a more rapid time to peak concentration with oral and sublingual than vaginal or rectal administration, highest peak concentrations with sublingual, and greatest area under the time curve with sublingual and vaginal administration.

Physiological studies

Chong *et al.*[9] measured intrauterine pressures in 57 healthy women after delivery. After 30 minutes of baseline recording, the women sequentially received syntometrine 1 mL or misoprostol 200, 400, 500, 600 or 800 μg (10 per group except the last, with 7). One woman receiving 800 μg developed severe hyperthermia. The onset of increased uterine activity was significantly slower with misoprostol than with syntometrine. There were no significant differences between groups for the increase in uterine activity or the duration of action. Danielsson *et al.*[4] studied intrauterine pressure in 30 women after administration of 200 or 400 μg misoprostol orally or vaginally in the first trimester of pregnancy. Time to onset and to maximum tonus respectively were as follows: 400 μg orally: 7.8 (3.0) and 25.5 (5.0); 400 μg vaginally: 20.9 (5.3) and 46.3 (20.7) minutes. The initial increase in tonus was more pronounced after oral than after vaginal administration. Aronsson *et al.*[10] studied intrauterine pressure in 32 women at 8 to 11 weeks of gestation, for 4 hours following misoprostol 400 μg orally, vaginally or sublingually. The time to increased tonus was shorter with oral (7.8) and sublingual (10.7–11.5) than with the vaginal route (19.4 minutes). The time to maximum tonus was also shorter (39.5, 47.1–51.7 and 62.2 minutes, respectively). Increase in uterine activity after 2 hours was greater for the sublingual and vaginal route than the oral route.

Labour induction studies

To evaluate the relative clinical efficacy of misoprostol by various routes, randomised clinical trials in which similar dosages of misoprostol were administered by different routes for labour induction at term were systematically reviewed.

Table 2. Qualitative comparisons of various routes of administration of misoprostol.

	Route				
	Oral	Vaginal	Rectal	Sublingual	Intrauterine
Pharmacokinetic studies					
Onset	Rapid	Slower	Slower	Rapid	
Peak	High	Lower	Lower	Highest	
Duration	Short	Long	Long	Long	
Total bioavailability	Low	2–3 × oral	1.5 × oral	Highest	
Clinical studies for induction of labour					
Efficacy	Moderate	Better than oral	Similar to vaginal	Better than oral	
Intrauterine pressure studies					
First trimester	Rapid onset. Rapid time to peak	Slower onset and time to peak. More prolonged activity		Rapid onset. Prolonged activity.	
After delivery	Rapid onset (6 minutes). Duration 75 minutes.				
Clinical studies prophylactically after delivery					
Efficacy	Less than syntocinon	No studies	Insufficient data		
Pyrexia and shivering	Common		Less than oral		
Theoretical considerations: use for treatment of PPH					
Administration	Easy	Not feasible	Easy even if not conscious	Relatively easy if conscious	Invasive
Likely efficacy	Fast onset, limited duration	Slow onset	Slow onset	Good	Unknown
Advantages	Convenient, rapid onset of action		Relatively convenient	Best pharmacokinetic profile	Possible local effect
Side effects	Prominent	Unknown	Apparently less than oral	Unknown	Likely to be low relative to effect

Table 3. Randomised controlled trials of misoprostol for treatment of PPH.

Study	Randomisation	Participants	Interventions	Notes
South Africa 2001[20]	Random allocation by sealed sequentially numbered envelopes.	64 women with primary PPH >500 mL in two centres.	Experimental: 800 μg (4 tablets) misoprostol per rectum + a placebo intramuscular injection + placebo crystalloid intravenous infusion. Control: Syntometrine + syntocinon intravenous infusion + 4 placebo tablets per rectum.	Single blinded study as obstetricians were aware of the type of drug being given. Patients and midwives were blinded. No mention of drugs used in the third stage and measurement of blood loss.
Gambia 2004[18]	Next in a series of randomised treatment packs in opaque envelopes with 3 tablets of misoprostol 200 μg or placebo.	160 women with measured postpartum blood loss of 500 mL or more and inadequate uterine contraction thought to be a possible factor.	Routine third stage management with oxytocin 10 units or syntometrine 1 ampoule. Misoprostol (200 μg) or placebo tablets administered one orally, two sublingually.	Blinding may have been compromised by non-identical placebos.
South Africa 2004[19]	Treatment packs containing 5 tablets of independently ordered in computer-generated random sequence and numbered consecutively.	244 women with bleeding more than expected at least 10 minutes after delivery thought to be due to uterine atony and requiring additional uterotonic therapy.	Routine third stage management with oxytocin 10 units or syntometrine 1 ampoule. Trial tablets (misoprostol 200 μg or placebo) administered 1 orally, 2 sublingually and 2 rectally.	6/244 data sheets did not have pack numbers completed and could not be included in analysis. No abnormal outcomes in these 6 exclusions except 1 case of shivering and 1 of blood transfusion.

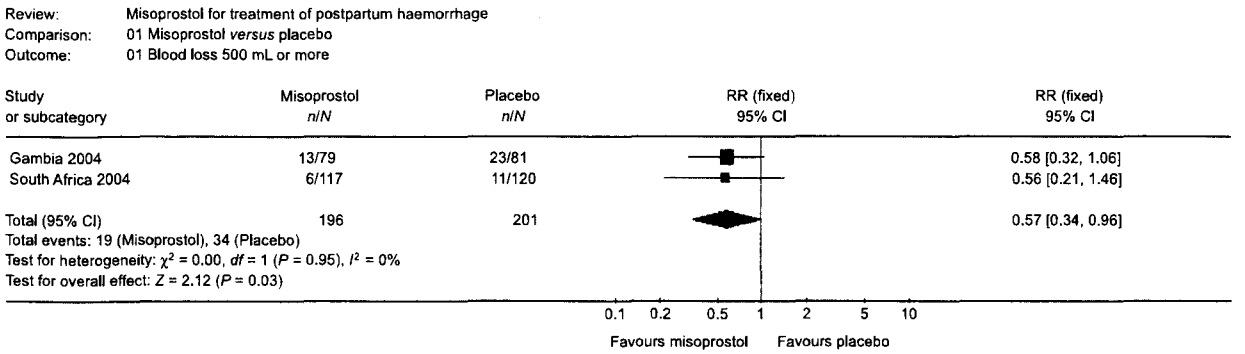

Fig. 1. The effect of misoprostol on measured blood loss of 500 mL or more after enrolment.

Outcomes related to the uterine activity response to misoprostol were compared. Data were combined using Revman software and a fixed-effects model (there was no significant heterogeneity).

In four studies (548 women),[11–14] induction or randomisation to delivery time was less with the vaginal than with the oral route (weighted mean difference −4.8, 95% CI −6.4 to −3.2 hours). In three studies (587 women),[12,13,15] failed vaginal delivery in 24 hours was less with the vaginal than with the oral route (RR 0.60, 95% CI 0.49 to 0.73). In one study[16] (100 women), failed vaginal delivery in 24 hours was less with the sublingual than the oral route (RR 0.56, 95% CI 0.37 to 0.84), as was the induction to delivery time (mean difference −8.3, 95% CI −15.4 to −1.2 hours). Overall, there was consistently greater clinical efficacy, at equivalent doses, with the vaginal and sublingual routes than with the oral route. In one small study, similar efficacy for labour induction was found when misoprostol was administered vaginally and rectally.[17]

Systematic review of randomised controlled trials of misoprostol for the treatment of PPH

Three studies were identified. Two studies compared misoprostol with placebo after routine treatment with conventional uterotonics[18,19] and one study[20] compared rectal misoprostol with oxytocin/ergometrine (Table 3).

Misoprostol *versus* placebo

Of the three primary outcomes, the only statistically significant difference was a reduction in blood loss of 500 mL or more by 43% (RR 0.57, 95% CI 0.34 to 0.96) (Figs 1–3; Tables 3 and 4). All secondary outcomes were similar, except for a considerable increase in pyrexia (RR 6.4, 95% CI 1.7 to 24) and shivering (RR 2.3, 95% CI 1.7 to 3.2) after misoprostol.

Misoprostol *versus* oxytocin/ergometrine

In one study,[20] 64 women with primary PPH were treated in a single-blind trial with misoprostol 800 μg rectally or syntometrine (oxytocin 5 units plus ergometrine 0.5 mg) intramuscularly plus oxytocin by intravenous infusion (Table 3). Subjective cessation of haemorrhage within 20 minutes occurred in 30/32 of the misoprostol group and 21/32 of the syntometrine/oxytocin group (RR 0.18, 95% CI 0.04 to 0.76).

Discussion

There is no doubt that misoprostol has strong uterotonic effects. In the context of PPH, the question is whether a route and dose can be found with absorption within a

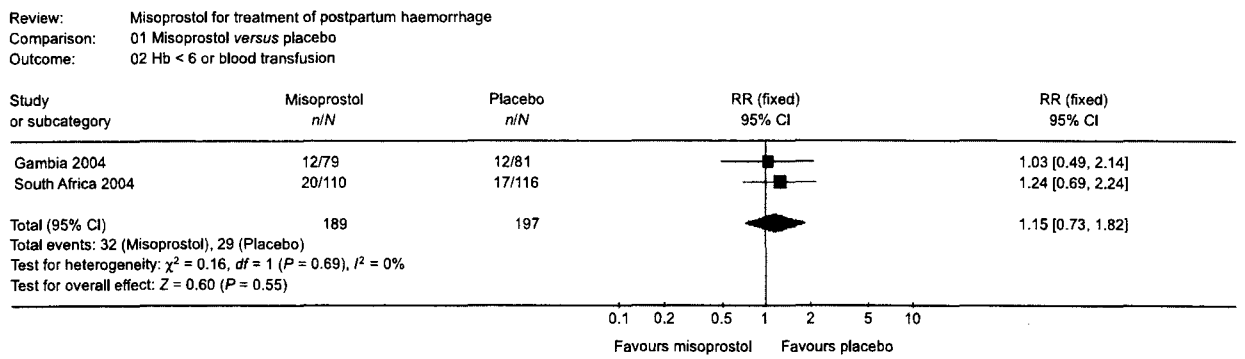

Fig. 2. The effect of misoprostol on postpartum haemoglobin level <6 g/dL or blood transfusion.

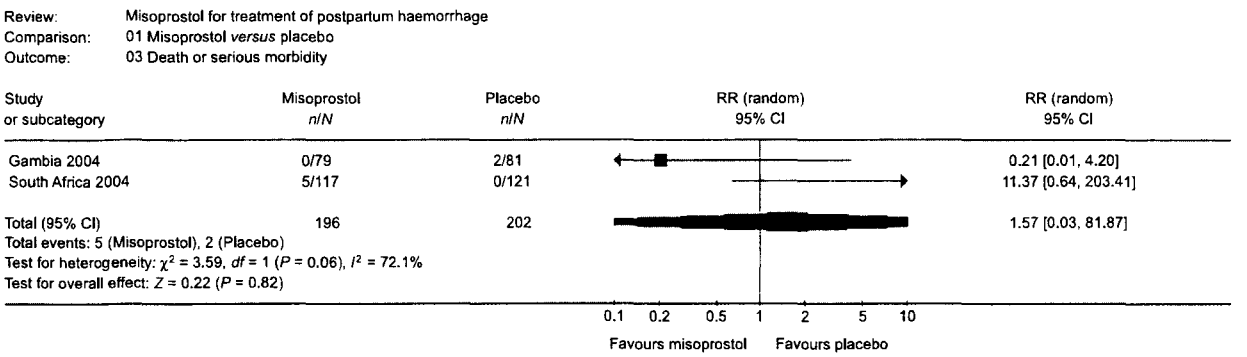

Fig. 3. The effect of misoprostol on maternal death or serious morbidity.

meaningful time, a clinically significant effect and acceptable side effects. The pharmacokinetic data to date indicate that oral and sublingual routes have the advantage of rapid onset of action, while the sublingual, vaginal and rectal routes have the advantage of prolonged activity and greater bioavailability. The increased bioavailability of non-oral routes is thought to be contributed to by the avoidance of the first pass intestinal–hepatic circulation. As clearance of the drug is likely to be rapid irrespective of the route of administration, the prolonged activity of the vaginal and sublingual routes is presumably due to continued absorption over an extended period. Duration of absorption is therefore likely to correlate with the retention of the tablet in the respective site over time. This may be a limitation of the sublingual route in an unstable or unconscious patient. The vaginal route is unlikely to be suitable for management of PPH because of the difficulty of ensuring retention in the vagina and absorption in the presence of vaginal bleeding.

The physiological studies reviewed showed more rapid onset of uterine activity with oral and sublingual than with vaginal administration of misoprostol, and more sustained effects with the sublingual and vaginal routes. In the oral groups, no statistically significant difference in uterine contractility was demonstrated for dosages ranging from 200 to 800 μg.

Clinical trials during pregnancy have shown that, at equivalent dosage, the vaginal and sublingual routes produce greater clinical efficacy than the oral route, and the rectal route is possibly similar to the vaginal route.

There have been several case reports[21–26] and one randomised controlled trial reviewed here[20] of dramatic effects of misoprostol in the treatment of PPH, assessed subjectively and unblinded. Our meta-analysis, placebo-controlled, double-blind, randomised, controlled trials showed less dramatic effect than reported previously. However, this is the first report to document a statistically significant reduction in objectively measured blood loss with misoprostol used for the treatment of PPH. Possible reasons for less dramatic effects include:

1. Differences in dosages and routes of administration. The previous reports used 800 to 1000 μg or 200 μg rectally, 400 μg orally or 800 μg intrauterine. The dosage in the South Africa 2004 study[19] (200 orally, 400 sublingually and 400 rectally) is likely to have yielded blood levels similar to or greater than the rectal dosages used. The possibility of a qualitative difference between oral/sublingual and rectal routes should be considered, but there is no obvious biological basis for this.
2. The outcome measures used. In the placebo-controlled trials, blood loss was measured objectively, whereas in most of the previous reports the response to treatment was assessed subjectively. In addition, the lack of blinding in previous reports may have affected outcome assessment.

The relative risk reduction of blood loss of 500 mL or more was similar in the two placebo-controlled trials, despite

Table 4. Misoprostol *versus* placebo in women with PPH (see Figs 1–3 for other outcomes).

Outcome	Gambia 2004		South Africa 2004		Relative risk (WMD)	95% CI
	Misoprostol	Placebo	Misoprostol	Placebo		
Blood loss after enrolment (mL, SD)	325 (264)	410 (397)	168 (163)	176 (173)	(−19)	−58 to 21
Blood loss ≥1000 mL after enrolment	2/79	5/81	1/117	0/120	0.65	0.17 to 2.4
Additional uterotonics	3/79	5/81	63/111	63/112	0.96	0.58 to 1.6
Maternal death	0/79	0/81	3/117	0/121	7.2	0.38 to 139
Blood transfusion	12/79	9/81	19/115	15/119	1.3	0.81 to 2.2
Headache	7/79	11/81			0.62	0.23 to 1.7
Nausea	3/79	5/81			0.60	0.14 to 2.6
Shivering	23/79	8/81	63/116	30/118	2.3	1.7 to 3.2
Pyrexia ≥38.5°C	4/79	0/81	11/114	2/118	6.4	1.7 to 24

a lower dosage regimen in the Gambian trial. This is consistent with the finding of similar physiological measurements of postpartum uterine contraction pressures following misoprostol dosages ranging from 200 to 800 μg orally.[9] There is at present no good clinical evidence to support large dosages of misoprostol for the treatment of PPH.

Hyperpyrexia has been reported following misoprostol 800 μg orally.[9] In the recent South African trial[19] (200 orally, 400 sublingually and 400 rectally), three women had pyrexia ≥40°C. In the Gambia trial[18] (200 orally and 400 sublingually), 2/79 women had pyrexia ≥39°C and none ≥40°C. To minimise the risk of potentially dangerous side effects, future research should aim to identify the minimum dosage which is clinically most effective.

Conclusions

Misoprostol in a dosage of at least 200 μg orally plus 400 μg sublingually significantly reduces the incidence of measured ongoing blood loss of 500 mL or more in women with clinically diagnosed PPH. Because of the enormous potential impact on maternal health in poor countries, further research aiming to evaluate effects of misoprostol on substantive health outcomes, its safety and the optimal route and dosage is of the utmost urgency. Further pharmacological data are needed, particularly relating to the rectal and intrauterine routes of administration, and the interaction between misoprostol and other oxytocics. Trials of the use of misoprostol for treatment of PPH should be randomised and double-blinded to reduce the risk of bias in assessment of outcomes. Based on our systematic review, potential routes of administration include oral, sublingual, rectal or a combination of these. Dosage by the oral route should not exceed 600 μg because of the risk of hyperpyrexia. A regimen of 200 μg orally plus 200–400 μg sublingually or rectally, or 200–400 μg sublingually or rectally, would seem good options. There are very limited data on the intrauterine route, but the single case report is sufficiently interesting to justify further research.

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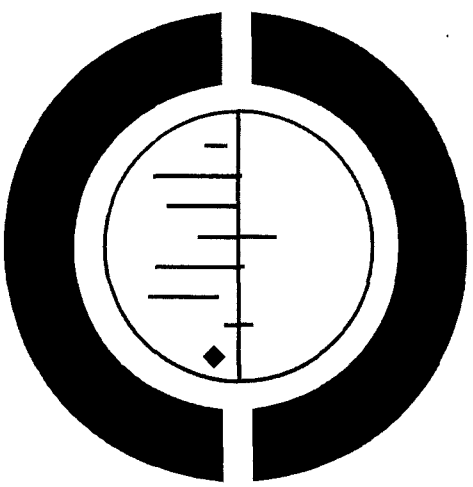
33.

Prostaglandins for preventing postpartum haemorrhage (Review)

Gülmezoglu AM, Forna F, Villar J, Hofmeyr GJ



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[Intervention Review]

Prostaglandins for preventing postpartum haemorrhage

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ABSTRACT

Background

Prostaglandins have mainly been used for postpartum haemorrhage (PPH) when other measures fail. Misoprostol, a new and inexpensive prostaglandin E1 analogue, has been suggested as an alternative for routine management of the third stage of labour.

Objectives

To assess the effects of prophylactic prostaglandin use in the third stage of labour.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (February 2007) and PubMed (July 2006). We updated the search of the Cochrane Pregnancy and Childbirth Group's Trials Register on 7 January 2011 and added the results to the awaiting classification section.

Selection criteria

Randomized trials comparing a prostaglandin agent with another uterotonic or no prophylactic uterotonic (nothing or placebo) as part of management of the third stage of labour. The primary outcomes were blood loss 1000 ml or more and the use of additional uterotonics.

Data collection and analysis

Two review authors independently assessed eligibility and trial quality and extracted data.

Main results

Thirty-seven misoprostol and nine intramuscular prostaglandin trials (42,621 women) were included. Oral (seven trials, 2849 women) or sublingual misoprostol (relative risk (RR) 0.66; 95% confidence interval (CI) 0.45 to 0.98; one trial, 661 women) compared to placebo may be effective in reducing severe PPH and blood transfusion (RR 0.31; 95% CI 0.10 to 0.94; five oral misoprostol trials, 3519 women). The severe PPH analysis of oral misoprostol trials was not totalled due to significant heterogeneity.

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Compared to conventional injectable uterotonics, oral misoprostol was associated with higher risk of severe PPH (RR 1.32; 95% CI 1.16 to 1.51; 16 trials, 29,042 women) and use of additional uterotonics but with fewer blood transfusions (RR 0.81; 95% CI 0.64 to 1.02; 15 trials, 27,858 women). Additional uterotonic data were not totalled due to heterogeneity. Misoprostol use is associated with significant increases in shivering and a temperature of 38 °Celsius.

There are scarce data comparing injectable prostaglandins with the conventional injectable uterotonics on severe PPH and the use of additional uterotonics, the primary outcomes of this review.

Authors' conclusions

Misoprostol orally or sublingually at a dose of 600 mcg shows promising results when compared to placebo in reducing blood loss after delivery. The margin of benefit may be affected by whether other components of management of the third stage of labour are used or not. As side-effects are dose-related, research should be directed towards establishing the lowest effective dose for routine use, and the optimal route of administration.

Neither intramuscular prostaglandins nor misoprostol are preferable to conventional injectable uterotonics as part of the management of the third stage of labour especially for low-risk women.

[Note: The 52 citations in the awaiting classification section of the review may alter the conclusions of the review once assessed.]

PLAIN LANGUAGE SUMMARY

Prostaglandins for preventing postpartum haemorrhage

Injectable uterotonic is the drug of choice for routine third stage management. Misoprostol may be used where no injectable uterotonic is available.

After her baby is born, the woman's womb (uterus) muscles contract and bleeding decreases. If the womb does not contract, postpartum haemorrhage (heavy bleeding) can occur, which can be life threatening. Prostaglandin, oxytocin and ergometrine are drugs that cause contractions of the womb (uterotonics). The review of 46 trials, involving 42,621 women, found that oral or sublingual prostaglandin (misoprostol) may be useful in places where injectable uterotonics are not available, and is not as effective as oxytocin and has more side-effects. The main side-effects are shivering and high temperature occurring in a significant proportion of women. Injectable prostaglandin may be effective in reducing blood loss but has adverse effects and costs more.

BACKGROUND

Postpartum haemorrhage (PPH) is a major cause of morbidity and mortality during childbirth, especially in low- and middle-income countries. The contribution of PPH to maternal death in low- and middle-income countries is more marked in domiciliary or rural settings where trained staff are scarce, transport facilities are inadequate and the availability of uterotonic agents and blood are limited. In a community-based study in Zimbabwe, PPH was the leading cause of maternal death in rural (40 per 100,000) but not urban (eight per 100,000) women (Fawcus 1995).

The third stage of labour is defined as the period from delivery of the baby until the delivery of the placenta and its membranes. This stage usually takes less than 10 minutes when active management is used. Active management of the third stage of labour is a term to express the use of uterotonics, early cord clamping and active efforts to deliver the placenta following delivery. It is not always clearly defined and universally applied in a standard manner. PPH is usually defined as blood loss of 500 ml or more and severe PPH as 1000 ml or more in the third stage of labour. The 'normal' amount of blood loss is difficult to ascertain because different ways of managing the third stage and assessing the blood loss lead to markedly different amounts. It is well demonstrated that active management of the third stage of labour is associated with less blood loss. There seems to be general agreement that if the blood loss exceeds 500 ml close monitoring and additional measures such as administering uterotonics or checking for a cause of bleeding are prudent measures.

Traditionally, oxytocin and ergot preparations have been used as

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uterotonic agents for PPH prophylaxis mostly as part of active management of the third stage of labour. These agents, although effective in decreasing the blood loss, have the disadvantage of instability in tropical climates (Hogerzeil 1996) and also require syringes and trained personnel for administration. Another disadvantage, mainly related to ergot preparations, is the relatively high incidence of side-effects such as nausea, vomiting and increase in blood pressure.

Prostaglandins have strong uterotonic properties and are used widely in obstetric and gynaecological practice for cervical ripening, together with mifepristone for termination of pregnancy and for induction of labour. Prostaglandin preparations are available in injectable, tablet or gel forms according to their intended use. These agents do not cause hypertension, which enables them to be used in hypertensive patients. In the management of the third stage of labour, prostaglandins have been mainly used for intractable PPH as a last resort when other measures fail. To date, the main disadvantages of prostaglandins have been their cost and availability. Recently, misoprostol, a prostaglandin E1 analogue used orally for the prevention of peptic ulcer disease has also been reported for use in the management of the third stage of labour (El-Refaey 1997). Misoprostol is inexpensive, administered orally and stable at ambient temperatures. There is considerable experience with misoprostol use, both for peptic ulcer disease and as a uterotonic in obstetrics and gynaecology. The main side-effects of prostaglandins are nausea, vomiting and diarrhoea. Shivering and elevated body temperature have been reported with the use of misoprostol in the third stage of labour.

The use of prostaglandins in general, and of misoprostol in particular, could have implications for the efficacy and acceptability of active management of the third stage of labour. The rate and nature of side-effects (nausea, vomiting, diarrhoea, shivering) could influence the immediate relationship between the mother and her baby in the hours following birth.

Active management of the third stage of labour (by use of uterotonics, early cord clamping and active efforts to deliver the placenta) decreases blood loss during the third stage of labour (Prendiville 2000). This review is one in a series of reviews evaluating strategies to prevent PPH (Cotter 2001; McDonald 2004; Prendiville 2000) and focuses on the role prostaglandins in the active management of the third stage of labour.

OBJECTIVES

To determine the effectiveness of prophylactic prostaglandin use compared to placebo or conventional uterotonics as part of the routine management of the third stage of labour.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials with a comparison between a prostaglandin and either another uterotonic agent or no uterotonic agent (placebo or nothing) were considered for inclusion in the review.

Types of participants

Women after delivery of the baby were the participants of this review. These women may be at high or low risk for postpartum haemorrhage. The definitions of high risk used by the trialists are accepted in general. These typically include having had a previous PPH, grand multiparity and multiple pregnancy among others. Data relating to high- and low-risk women are analysed separately as well as together (totals). Recent trials (mostly misoprostol) focused on a general population of women with vaginal or caesarean section delivery without specifying any risk status. Therefore, the high- and low-risk subgroupings were not used in the misoprostol comparisons. However, if future trials falling into these comparisons specifically study a risk group these subgroups will be added to the list of comparisons.

If a particular (risk) group is not specified, this implies that all women are included in that analysis regardless of their risk status. Studies that do not specify the risk status of women included are put in the low-risk category where such distinctions are made.

Studies including women with caesarean deliveries were eligible.

Types of interventions

In the earlier version of this review we included the use of prostaglandins when used 'as part of active management of the third stage of labour'. Recently, there has been increasing interest in evaluating the individual components of the 'active management' package and at least one trial that evaluated the use of a uterotonic without other components of active management of the third stage of labour. We included the use of only a prostaglandin within the scope of this review.

The experimental intervention evaluated in this review is the prophylactic use of prostaglandins in the management of the third stage of labour. Prostaglandin preparations are currently available in injectable and tablet forms, therefore different routes may be used and compared either with each other or with conventional injectable uterotonic agents. Different routes of administration are analysed in separate comparisons.

The choice of routine uterotonic drug used during the third stage of labour varies greatly around the world. In this review, oxytocin (Syntocinon®), ergometrine-oxytocin (Syntometrine®) and ergometrine are grouped together as 'conventional injectable uterotonics'. In cases where comparison is made with two different types

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of conventional uterotonics, oxytocin is selected as the conventional uterotonic as it is the drug used in most of the studies included in this review.

The main categories of prostaglandins evaluated in the review are misoprostol (prostaglandin E1 analogue), which is available in tablets and PGF2alpha and E2 preparations that are administered parenterally for use in the third stage of labour. Misoprostol tablets are administered either by mouth or rectally. Since the absorption of misoprostol from these two routes is currently unknown and likely to be different, these routes have been evaluated separately. Injection of oxytocin or saline, or both, into the umbilical vein (reviewed elsewhere on retained placenta) and intramyometrial injection of prostaglandins other than at caesarean section (not used for routine active management) were not eligible for inclusion in this review.

The following comparisons have been used in the review:

1. oral misoprostol versus no uterotonic/placebo;
2. oral misoprostol versus injectable (conventional) uterotonics;
3. rectal misoprostol versus no uterotonic/placebo;
4. rectal misoprostol versus injectable uterotonics;
5. rectal misoprostol versus intramuscular prostaglandins;
6. sublingual misoprostol versus no uterotonics/placebo;
7. sublingual misoprostol versus injectable uterotonics;
8. intramuscular prostaglandins versus rectal misoprostol;
9. intramuscular prostaglandin versus no uterotonic/placebo;
10. intramuscular prostaglandin versus injectable uterotonics;
11. comparisons of different prostaglandins or different dose/routes of the same prostaglandin;
12. comparisons of different prostaglandins plus injectable uterotonics versus injectable uterotonics or other prostaglandins.

Types of outcome measures

The primary outcomes of this review are blood loss of 1000 ml or more and the use of additional uterotonics in the third stage of labour. Maternal death is included as an outcome but it is unlikely that the review will have power to evaluate this outcome.

A. Outcomes related to blood loss

Reported blood loss is influenced by the assessment technique. Measurement of blood and clots in jars and weighing of linen are likely to be more precise than clinical estimation used in some studies. The latter is known to underestimate blood loss (Andolina 1999). Also, the duration of measurement and reporting the amount as 'greater than' or 'greater than or equal to' a certain cut-off level (e.g. 500 or 1000 ml) may affect the total reported amount of blood loss especially when this amount is estimated.

1. Postpartum haemorrhage (at least 500 ml);
2. severe postpartum haemorrhage (at least 1000 ml);
3. mean blood loss (ml);
4. use of additional uterotonics;
5. blood transfusion;
6. manual removal of placenta;
7. duration of third stage (minutes);
8. third stage longer than 30 minutes.

B. Side-effects

1. Any side-effect reported;
2. any side-effect requiring treatment;
3. nausea;
4. vomiting;
5. diarrhoea;
6. headache;
7. abdominal pain;
8. high blood pressure;
9. shivering;
10. severe shivering;
11. pyrexia (at least 38 °C);
12. severe pyrexia (at least 40 °C);
13. other.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (June 2008). We updated this search on 7 January 2011 and added the results to Studies awaiting classification.

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

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

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

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

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In addition, we searched PubMed with the search term 'misoprostol' in July 2006.
We did not apply any language restrictions.

Data collection and analysis

Two review authors independently evaluated trials under consideration for methodological quality and appropriateness for inclusion without consideration of their results. No language preferences were applied either during the search or selection of trials. Two authors independently extracted data regardless of whether they participated in a particular included trial or not.
We assessed methodological quality in terms of adequacy of allocation concealment as described in Higgins 2005.
In addition to the main outcomes, we systematically extracted the following data for each study:

1. trial entry criteria (high versus low risk, other specific exclusion criteria);
2. exclusions and missing data after randomization;
3. management of the third stage of labour;
4. the duration and technique of assessment of blood loss.

We evaluated statistical heterogeneity across trial results using the chi-square test as calculated in MetaView. Whenever statistical ($P < 0.1$) or visual heterogeneity was encountered, we explored the possible reasons. In meta-analyses with significant heterogeneity (statistical or visual), we discuss the trials individually (i.e. without totals).
It is not clear how components of third stage management, other than the uterotonic, affect the blood loss. While the comparison of the uterotonic might be valid, if other components of active management are effective, then the scope for any difference between a prostaglandin and a placebo or another uterotonic could be minimized if those components are used.
These factors are assessed as possible sources of heterogeneity where appropriate and if there are adequate numbers of studies to allow such assessments.
Because of the significant differences in pharmacokinetics and possibly other properties, we analysed oral, rectal, sublingual and buccal misoprostol and intramuscular prostaglandins (PGF2alpha and synthetic E2) separately.
We did not exclude trials on the basis of a predetermined cut-off value for loss to follow ups and postrandomization exclusions. We systematically extracted this information and discussed as appropriate for each trial.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
Seventy-five trials were identified and considered for inclusion in this review. Twenty-nine were excluded (*see* 'Characteristics of excluded studies' table). Altogether, 46 trials were included, involving 42,621 women - *see* 'Characteristics of includes studies' for details. Of these, 37 evaluated misoprostol and the remainder evaluated injectable prostaglandins (seven PGF2alpha and two PGE2). One trial compared misoprostol with intramuscular prostaglandin. (Forty-five reports from an updated search in January 2011 have been added to Studies awaiting classification.)

Settings

The review includes trials conducted in all continents from both low- to middle-income countries and industrialized countries. Twenty-seven trials included centres in low- and middle-income countries only. The WHO 2001 trial was conducted in nine countries in Africa, Asia, Europe and Latin America. In Africa, seven countries contributed 14 trials (five in South Africa). Eight trials were conducted in India.
The WHO 2001 trial is the largest trial in the review with 18,530 participants from nine countries. The WHO 1999 trial is a pilot dose-finding trial which preceded the WHO 2001 trial and used the same protocol. Side-effects of misoprostol during the first hour after delivery from the WHO 2001 trial are included in the meta-analyses, but further data describing side-effects in the first 24 hours after delivery were published in a separate article and are described in the results section.
Most trials (423/46) were conducted in hospitals where deliveries were performed by skilled caregivers. The Gambia trial (Gambia 2005) was conducted at the community level. Traditional birth attendants trained in trial procedures and blood loss measurement provided the interventions (oral misoprostol and oral ergometrine). In the Guinea-Bissau 2005 trial, trained midwives administered sublingual misoprostol or placebo to women delivering at primary care centres. In the India 2006c trial, auxiliary nurse-midwives administered oral misoprostol or placebo tablets to women delivering either at primary care centres (approximately 55%) or at home (approximately 45%).

Management of the third stage of labour

In 28 trials, the third stage was managed actively (at least two of the components of active management described, or specified as 'active'); two trials used 'passive management' (Holland 1991; India 2006c); nine trials did not mention and two were mixed with components of both active or passive management used. The remainder included women with caesarean section deliveries and did not report any particular form of management.

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Risk status

Three studies specifically studied women who were at high risk for postpartum haemorrhage (PPH) (Egypt 1997; Holland 1995; India 2001b). The participants were classified as high risk if they had a history of PPH or conditions such as multiple pregnancy and grand multiparity.

Mode of delivery

Five trials included only caesarean section deliveries (India 2006a; United Kingdom 1994; United Kingdom 2001b; USA 1990; USA 2005).

Blood loss assessment

The majority of the trials (n = 24) used some form of measurement, some using detailed weighing and hematin-dye techniques. Clinical estimation was used in 16 trials, haemoglobin change or level, or both, was used in three and no method was mentioned in the remaining three trials (Colombia 2002; India 2001b; India 2005a).

Comparisons

Of the 46 trials included in the review, 37 evaluated misoprostol in doses ranging from 50 mcg to 800 mcg and using oral, sublingual, buccal and rectal routes. Misoprostol was compared to placebo in nine trials (France 2001; Gambia 2005; Guinea-Bissau 2005; India 2006c; South Africa 1998b; South Africa 1998c; South Africa 1998d; South Africa 2001; Switzerland 1999) and to conventional injectable uterotonics in 25 trials. The uterotonic agent was oxytocin 10 international units (IU) intramuscularly in most of these trials. In some trials the uterotonic group received oxytocin or ergometrine-oxytocin depending on the hospital routine (Australia 1999) or depending on whether the woman was hypertensive or not (United Kingdom 2000).

Some trials had several treatment arms. One of the intramuscular prostaglandin trials (Holland 1991) and two misoprostol trials (France 2001; South Africa 1998d) had three arms, one of which was a placebo control group. The WHO 1999 trial is also a three-arm trial comparing misoprostol 600 mcg, 400 mcg orally and oxytocin 10 IU. The United Kingdom 2003 trial had three arms comparing oral misoprostol 600 mcg, rectal misoprostol 600 mcg, and rectal misoprostol 400 mcg.

Concurrent routine uterotonic use

Two trials from Turkey had four arms, comparing misoprostol 400 mcg after cord clamp followed by misoprostol 100 mcg at four and eight hours postpartum; the same regimen of misoprostol combined with intravenous oxytocin; intravenous oxytocin only; and intramuscular methyl ergometrine only. For blood loss and other early outcomes assessed before the follow-up doses of misoprostol were given, the dosage is regarded as 400 mcg. The only differences between these two trials were that Turkey 2002 used rectal misoprostol and Turkey 2003 used oral misoprostol. The USA 2004 and USA 2005 trials compared 200 mcg buccal misoprostol to placebo in women delivering vaginally and by caesarean section respectively. All women received 20 IU oxytocin infusion at a rate of 10 ml/minute for 30 minutes and then 125 ml/hour for eight hours.

The review includes unpublished data from Canada 2005, South Africa 1998d, WHO 1999, United Kingdom 2000 and WHO 2001 trials.

Risk of bias in included studies

Allocation concealment was considered adequate in thirty-two studies that used sealed envelopes, opaque containers, or identical numbered boxes containing trial medications. Holland 1995 had 15% of the women excluded after randomization, mostly due to women being randomized despite being ineligible (for augmentation of labour), and Turkey 2003 had 12.6% of the women excluded after randomization secondary to them requiring caesarean sections. There were an unspecified but small number of postrandomization exclusions in South Africa 1998a. These were due to hypertension being discovered after randomization, which resulted in exclusion of some women allocated to ergometrine-oxytocin.

In trials evaluating different interventions in the third stage of labour, postpartum haemorrhage (PPH) is often the primary outcome. Assessment of PPH is prone to bias if the staff making the assessments are not blind to the intervention. In this review, outcome assessments were blinded in nineteen trials. Some outcome assessments were blinded in two trials.

In this review, trials comparing misoprostol with other uterotonics are, in essence, equivalence trials designed to evaluate whether misoprostol is as effective as others given its advantage of oral or rectal route of administration. The majority of such trials have set relatively large margins of equivalence and are therefore, in practical terms, underpowered to test an equivalence hypothesis. The WHO 2001 trial is the largest trial in the review which set an a priori clinical equivalence margin (within 35% efficacy of oxytocin). In this trial the primary outcomes were blood loss greater than or equal to 1000 ml and the use of additional uterotonics. Misoprostol versus placebo or no treatment trials are non-equivalence trials and do not have the problem mentioned above.

The South African trials and the United Kingdom 2001b trial evaluating oral misoprostol used non-identical placebos. The women participating in the South African trials took the medications out of an opaque container with care being taken to conceal the tablets from midwives. Although this method of blinding is not 100% safe, the authors provided the review authors with the information

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that unblinding was unlikely to occur in the settings in which the trials were conducted. In the United Kingdom 2001b trial, side-effect assessments were blinded.

One study (Holland 1995) was stopped prematurely before reaching a prespecified interim analysis to determine an appropriate sample size. This was due to the manufacturer of the drug issuing a warning about serious cardiovascular side-effects after intramuscular use of sulprostone, a synthetic PGE2 derivative.

Effects of interventions

The results are based on 37 misoprostol and nine intramuscular prostaglandin trials.

Misoprostol trials

Primary outcomes

Misoprostol versus placebo/no treatment (nine trials, comparisons 01, 02, 04, 07, 20)

Oral misoprostol was used in seven trials(comparison 01: 5153 women total, 4253 in five 600 mcg trials), rectal (comparison 03), sublingual (06) and buccal (18) in one trial each. There were three maternal deaths in misoprostol and one in placebo groups overall in nine trials.

There was significant qualitative and statistical heterogeneity for the outcome severe postpartum haemorrhage (PPH) in the oral misoprostol versus placebo comparison. Earlier trials (France 2001; South Africa 1998d; South Africa 2001) did not indicate any reduction in severe PPH while the more recent Gambia 2005 (relative risk (RR) 0.48; 95% confidence interval (CI) 0.09 to 2.59, 2/629 versus 4/599) and India 2006c (RR 0.20; 95% CI 0.04 to 0.91, 2/812 versus 10/808) trials suggest some protective effect of misoprostol on severe PPH. The use of additional uterotonics was less when misoprostol was used in four out of six trials but not in the South Africa 1998d trial that had both 600 and 400 mcg treatment arms. Compared to placebo, oral misoprostol reduced blood transfusion (RR 0.31; 95% CI 0.10 to 0.94, five trials, 3519 women).

One rectal misoprostol trial using 400 mcg did not show statistically significant difference in severe PPH (RR 0.69; 95% CI 0.35 to 1.37).

The Guinea-Bissau trial used 600 mcg sublingual misoprostol and showed a statistically significant difference in reducing severe PPH (RR 0.66; 95% CI 0.45 to 0.98, 37/330 versus 56/331).

The USA 2004 and USA 2005 trials used 200 mcg buccal misoprostol in women undergoing vaginal delivery and caesarean section respectively. All women received 20 IU oxytocin infusion in 1 litre of saline. In the USA 2005 trial there were 24/173 versus 22/179 cases of severe PPH in the misoprostol and placebo groups respectively whereas there were no cases of severe PPH in the USA 2004 trial. In both trials the protocol included oxytocin infusion after delivery of the placenta.

Misoprostol versus conventional injectable uterotonics (25 trials, comparisons 03, 05, 08)

Sixteen trials compared oral misoprostol (comparison 03), five compared rectal (comparison 05) and four compared sublingual (comparison 08) to injectable uterotonics (oxytocin intramuscular or intravenous, ergometrine, ergometrine + oxytocin). Maternal deaths were reported only in the WHO 2001 trial (2/9264 versus 2/9266). There were no deaths in the Ghana 2006, Canada 2005, Turkey 2002 and WHO 1999 trials. Others did not mention whether there were any deaths or not.

Oral misoprostol was associated with a statistically significant higher risk of severe PPH (RR 1.32; 95% CI 1.16 to 1.51, 16 trials, 29,042 women). While the large WHO 2001 trial results dominate the meta-analysis the majority of trials show similar results with no statistically significant heterogeneity across different doses or trials. The use of additional uterotonics shows a similar trend but the results were not totalled because of significant statistical heterogeneity. There was a trend towards fewer blood transfusions with misoprostol (RR 0.81; 95% CI 0.64 to 1.02, 15 trials, 27,858 women).

Three rectal misoprostol versus injectables trials reported on severe PPH and there were similar numbers of women with this outcome in the two groups (RR 1.14; 95% CI 0.70 to 1.85, 1784 women). More women who received misoprostol required additional uterotonics (RR 1.64; 95% CI 1.16 to 2.31).

Four small trials compared sublingual misoprostol to injectables. The meta-analysis (graphs 08.02, 08.05) is too small to give any meaningful results.

Concurrent routine uterotonic use (Comparisons 16 and 18)

Oral and rectal misoprostol combined with oxytocin were compared to conventional uterotonics in the Turkey 2003 and Turkey 2002 trials respectively. Oral misoprostol when combined with oxytocin was more effective than placebo and oxytocin in decreasing severe PPH (RR 0.38; 95% CI 0.15 to 0.97), and PPH (RR 0.44; 95% CI 0.23 to 0.84). We were not able to use the additional uterotonic data from these trials.

Side-effects

Oral misoprostol 600 mcg was consistently associated with higher rates of prostaglandin-related side-effects such as nausea, vomiting, diarrhoea as well as for 'any' shivering, severe shivering and pyrexia (greater than 38 °C) when compared with placebo as well as with conventional uterotonics. We did not total most of these

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comparisons (graphs 01.17, 01.19, 02.18, 02.20) because of heterogeneity but the heterogeneity was quantitative, i.e. all studies showed an increase in these events. For 'any' shivering the individual trial RRs ranged between 1.43 to 69.10.

Further analysis of side-effects during the first 24 hours in the WHO 2001 trial showed that in comparison to oxytocin, women who received misoprostol had a higher incidence of 'any' shivering (RR 4.70; 95% CI 1.90 to 11.20), and of pyrexia (RR 6.3; 95% CI 3.70 to 10.80) in the period two to six hours after delivery. Diarrhoea was also more common in the misoprostol group in the period two to six hours (RR 21.00; 95% CI 5.10 to 86.50) and seven to 12 hours (RR 7.70; 95% CI 2.30 to 25.40).

The results of two trials (South Africa 1998d; WHO 1999) where 600 mcg and 400 mcg doses of oral misoprostol were compared indicate that side-effects are dose-related (any shivering RR 1.33; 95% CI 1.07 to 1.64) (Comparison 12.15). This might not apply, however, to rectal misoprostol, as there were no significant differences in the one trial (United Kingdom 2003) that evaluated 600 mcg and 400 mcg doses of rectal misoprostol. A comparison of 600 mcg rectal versus 600 mcg oral misoprostol in the same trial showed that rectal misoprostol had less pyrexia, 'any' shivering, and severe shivering (RR 0.27; 95% CI 0.16 to 0.46) (Comparison 14.08) than oral misoprostol.

Intramuscular prostaglandin trials (comparisons 09, 10, 11)

Ten trials compared injectable prostaglandins with conventional injectable uterotonics. One trial (Holland 1991) was a three-arm trial with a placebo arm in addition to sulprostone and oxytocin. The occurrence of primary outcomes such as blood loss 1000 ml or more and the use of additional uterotonics were too few to give reliable estimates.

Intramuscular prostaglandins had less mean blood loss when compared with no uterotonic use in one trial with 50 women (Holland 1991) that examined this outcome (-224 ml weighted mean difference; 95% CI -420.30 to -27.60 ml). Other outcomes evaluated in this study were not statistically significant.

When compared with conventional uterotonics, intramuscular prostaglandins had less blood loss and shorter duration of the third stage (-1.10 minutes weighted mean difference; 95% CI -1.40 to -0.89 minutes). Blood loss data were not totalled because of heterogeneity due to one small trial having result in the opposite direction. Three other trials showed less blood loss with injectable prostaglandin.

Vomiting, abdominal pain and diarrhoea were more common with intramuscular prostaglandins.

Intramuscular prostaglandin F2alpha was compared to rectal misoprostol 400 mcg in one small trial with 120 women (India 2006d). There were more women requiring additional uterotonics (2/60 versus 10/60) but the study was too small to give any guiding evidence. Another small trial compared intramyometrial injection of PGF2alpha with intramyometrial oxytocin to women having caesarean section deliveries (USA 1990).

DISCUSSION

This review includes comparisons of intramuscularly, orally, and rectally administered prostaglandins with placebo, and with conventional injectable uterotonics. We did not combine misoprostol with other prostaglandins in the meta-analyses. Misoprostol tablets are used via oral, rectal, sublingual or buccal routes while other prostaglandins are used intramuscularly (or intramyometrial during caesarean section). In terms of outcomes, we gave emphasis to blood loss of at least 1000 ml and the use of additional uterotonics as the most clinically relevant outcomes. We recorded maternal death data systematically but did not anticipate having sufficient power to analyse this outcome.

While the results of earlier trials comparing misoprostol (used orally or rectally) to placebo or no treatment were somewhat equivocal, the results of the recent trials are more promising (Gambia 2005, Guinea-Bissau 2005; India 2006c). It is important to note that all three recent trials have design and setting differences that make the summing up of their results difficult. The Gambia 2005 trial had lower than expected number of events and although the direction of effect favours misoprostol the trial is not powered adequately. In addition, oral ergometrine was assumed to be equivalent to placebo and although the value of oral ergometrine is questionable (WHO 1994), it may not be zero. The third stage management was 'active'. This trial is the only trial that used traditional birth attendants to administer the trial interventions. The Guinea-Bissau 2005 trial used sublingual misoprostol within the context of active management and showed greater effect with higher blood loss (i.e. 1000 ml compared to 500 ml). Almost half of the women in this trial (150/330 and 170/331 in the misoprostol and placebo groups) experienced blood loss of 500 ml or more which is unusual in PPH trials with active management. The India 2006c trial used oral misoprostol in the context of 'passive' management of the third stage of labour. Therefore, its findings are more applicable to settings where this type of third stage management is the norm. It is not known whether with other components of active management being in place the same magnitude of effect would hold or not.

With the addition of three non-hospital based trials, it is possible to make some inferences for those settings although all three trials have important differences. All three trials were conducted either at home or at primary care centres and it is reassuring to see that there were no major adverse events related to misoprostol use. The Guinea-Bissau and India trials were conducted by caregivers skilled in third stage management although only the former had fully qualified midwives.

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The addition of several smaller misoprostol versus injectable uterotonic trials confirm the findings of the earlier version of the review. Overall injectable uterotonics are more effective than misoprostol. Various injectables were used in the included trials. The data with regard to the comparative efficacy of oxytocin 10 international units (IU) versus ergometrine suggest that there are no major advantages of either of them (McDonald 2004). Ergot preparations seem to be somewhat more effective in reducing blood loss but are associated with a higher rate of side-effects and the choice should be made according to the trade-off between the benefit and harm (Carroli 2001).

The results of the large WHO 2001 trial, conducted in nine countries with the participation of 18,530 women, dominate the systematic review's comparison between misoprostol 600 mcg and injectable uterotonics, mostly 10 IU of oxytocin. This comparison demonstrates that oral misoprostol up to 600 mcg is associated with a higher risk of blood loss and the use of additional uterotonics (up to 16% of women will require additional uterotonic treatment) when compared with a policy of injectable uterotonics. There is a consistent increase in all prostaglandin-related side-effects. Considering that the observed rate of side-effects is already high, it is unlikely that higher doses of oral misoprostol (to increase efficacy) could be used for the routine prevention of postpartum haemorrhage among healthy women although the recent Ghana 2006 trial used 800 mcg misoprostol.

Although in almost all of the trials these side-effects were reported as not severe, they cause discomfort. For example, women in the WHO 2001 trial rated to have severe shivering needed extra blankets or other comfort measures. Amant reported that women who had shivering had their teeth chattering for 10 to 20 minutes and had no control over their body movements during this period (Amant 2001). On the other hand, in the case of pyrexia (greater than 38 °C), the staff may be concerned for the woman about the risk of postpartum infections and the need for initiating any unnecessary antibiotic treatment. Furthermore, fever may delay blood transfusion.

The largest trial (WHO 2001) used oxytocin both intramuscularly or intravenously. While it is obvious that intravenous injection provides faster availability of the drug, pharmacokinetic data show that with the intramuscular route oxytocin is circulating in the blood within two to three minutes (Gibbens 1972). Furthermore, the pharmacokinetics of oral misoprostol demonstrate that misoprostol acid reaches its peak in the plasma between 20 to 30 minutes after oral administration (Zieman 1997), well after the mean time from delivery until placental expulsion observed in the WHO 2001 (8.3 minutes, standard deviation (SD) 14.6) and Mozambique 2001 (9.0 minutes, SD 3.6) trials. Therefore, we do not think that the route of administration of oxytocin will affect its efficacy.

The three studies which enrolled women undergoing caesarean section deliveries have been included together with the others in the analysis. The amount of blood loss during and after caesarean section may be different, due to additional bleeding not directly related to the contractility of the uterus and, due to inevitable contamination with other fluids. However, a differential effect between different uterotonics is unlikely. Therefore, a sensitivity analysis according to the mode of delivery was not conducted. The problems associated with measurement of blood loss at caesarean section may, however, obscure any smaller differences in efficacy and push the results towards 'no difference'. In this review these studies were analysed within the group of studies which included women at low risk for postpartum haemorrhage.

With the data available so far there do not seem to be major differences between intramuscular prostaglandins and conventional injectable uterotonics (oxytocin or ergometrine) in reducing the blood loss in the third stage of labour. These trials had few women who experienced the primary outcomes of this review, although the mean blood loss (a secondary outcome) was reduced by 70 ml on average for women who received intramuscular prostaglandins. Vomiting and diarrhoea were common side-effects. The studies reported, however, that side-effects did not need treatment. The concerns of safety, cost and side-effects are important limitations of intramuscular prostaglandins.

The recent WHO systematic review on cause of maternal deaths identified obstetric haemorrhage as the largest cause of maternal death in Africa and Asia where the majority of maternal deaths occur (Khan 2006). Prevention of PPH with appropriate, evidence-based interventions such as oxytocin (and misoprostol when oxytocin is not available) could prevent a substantial proportion of deaths in these two regions.

AUTHORS' CONCLUSIONS

Implications for practice

The uterotonic of choice in settings where active management is practiced is oxytocin 10 IU administered intravenously or intramuscularly. Getting oxytocin used as widely as possible should be the primary aim for deliveries occurring outside hospitals at peripheral levels of the healthcare system or at home. Oxytocin retains more than 85% active drug after storage for one year at under 30 °Celsius and is less expensive than misoprostol in most settings. If these conditions for oxytocin use cannot be met then misoprostol could be used based on the current evidence. The empirical dosage most used in trials to date is 600 mcg orally. Promising results against placebo have also been reported in individual trials of 400 mcg orally (over and above the routine use of oxytocin), and 600 mcg sublingually.

More efforts should be devoted to making injectable uterotonics available especially using strategies such as that of disposable pre-

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filled syringes, e.g. Uniject (PATH 2001). Developing the skills to administer injections in areas where this is not currently available will have the additional benefit of enabling other effective treatments such as parenteral antibiotics or anticonvulsants to be used.

Intramuscular prostaglandins are not preferable to conventional uterotonics in the routine management of the third stage of labour especially for low-risk women.

Implications for research

The recent misoprostol versus placebo trials conducted outside hospitals that showed promising results should be replicated in order to strengthen the evidence base for justifying any use of misoprostol for routine third stage of labour management when conventional uterotonics are not available. As side-effects are dose-related and life-threatening hyperpyrexia has been reported with 800 mcg orally (Chong 1997), research should be directed towards establishing the lowest effective dose for routine use, and the optimal route of administration.

For the settings in which active management of the third stage is the norm, there is no need for further trials comparing misoprostol with injectable uterotonics. Future research in the third stage of labour could focus on investigating the effectiveness of the particular components of active management.

Intramuscular prostaglandins may be studied for the management of high-risk cases since they are unlikely to find widespread use in low-risk cases due to their costs and side-effects.

[Note: The 52 citations in the awaiting classification section of the review may alter the conclusions of the review once assessed.]

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CHARACTERISTICS OF STUDIES

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

Australia 1999

Methods	Random allocation from a table of random numbers with sequentially numbered, sealed, opaque envelopes. Block randomization was utilized. The study was not blinded
Participants	930 women with vaginal delivery in 4 centres in Australia, China, and Papua New Guinea. Exclusion criteria: coagulation disorders, asthma, severe renal disease, epilepsy, elective caesarean section, severe hypertension
Interventions	Misoprostol 400 mcg orally vs IM injection of either oxytocin (10 IU) (1 centre) or ergometrine-oxytocin (5 IU oxytocin + 0.5 mg ergometrine) (3 centres)
Outcomes	Blood loss, duration of third stage, use of additional uterotonics, blood transfusion, side-effects, haemoglobin level. Measurement of blood loss: by combining estimated (assessment by clinician) and measured (measuring volume with calibrated measuring jug, and weighing of linen). It is unclear if some centres used one or the other method
Notes	Management of third stage: no mention of third stage management technique. 31/455 (7%) were excluded after randomization in the misoprostol group, and 36/475 (8%) were excluded after randomization in the oxytocin/ergometrine-oxytocin group This trial was stopped after recruitment of 863/1862 women following the unsatisfactory results of an interim analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Belgium 1999

Methods	Random allocation from a computer-generated list of study numbers. Randomization in blocks. Identical numbered study boxes were used. Outcome assessments were blinded
Participants	213 women with vaginal delivery in Leuven, Belgium. Exclusion criteria: caesarean section, hypertensive disorders, gestational age < 32 weeks, intrauterine death, uterine malformations, allergy to prostaglandins or alkaloids, inflammatory bowel disease, coronary disease, vascular disease, sepsis
Interventions	Misoprostol 600 mcg orally vs methylergometrine 200 mcg IV. Both oral and IV placebos were used
Outcomes	Blood loss, need for additional uterotonics, side-effects. Blood loss was estimated.

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Belgium 1999 *(Continued)*

Notes	Management of third stage: uterine massage, cord traction, manual removal of placenta after 30-60 minutes. 5/100 (5%) were excluded after randomization in the misoprostol group, and 8/108 (7.4%) were excluded in the methylergometrine group

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Canada 2002

Methods	Random allocation from a central centre statistician using block randomization for each participating centre. Consecutively-numbered opaque, sealed packets for allocation concealment. No blinding of treatment or outcome assessments
Participants	223 women with vaginal delivery from 3 hospitals in Toronto, Canada. Exclusion criteria: parity > 6, gestational age < 32 wks, clotting disorder, anticoagulant therapy, history of postpartum haemorrhage, previous caesarean delivery
Interventions	Misoprostol 400 mcg rectally after delivery vs oxytocin 5 IU IV or IM, or 10 IU IM given after delivery (sometimes given after placenta delivered)
Outcomes	Blood loss was captured by measuring change in measured haemoglobin. Other outcomes were duration of third stage, need for additional uterotonics, manual removal of placenta, blood transfusion, side-effects
Notes	No description of third stage management. 13 women excluded after randomization secondary to having a caesarean section. 2 women lost to follow up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Canada 2005

Methods	Randomized double blind, no further details. Unclear if outcome assessments were blinded
Participants	622 women with vaginal delivery at a university hospital in Halifax, Nova Scotia, Canada. Women with multiple pregnancy, placenta previa, abruptio placentae, coagulation abnormalities, caesarean delivery and asthma were excluded
Interventions	Misoprostol 400 mcg orally after delivery of anterior shoulder vs oxytocin 5 IU IV

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Canada 2005 (*Continued*)

Outcomes	Blood loss measured by haematocrit drop greater than 10%, haemoglobin drop greater than 30%, additional uterotonics, blood loss greater than 1000 ml and 500 ml
Notes	Third stage management was 'active'. No mention of postrandomization exclusion or loss to follow up. The authors attribute the high numbers of additional uterotonic use to most women having IV lines during labour and the threshold for bolus oxytocin administration being low

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

China 2004a

Methods	Open, randomized trial. Randomization generated by a random-number table. Unclear if outcome assessments were blinded
Participants	60 low-risk women delivering vaginally in Hong Kong, China.
Interventions	Misoprostol 600 mcg sublingually vs syntometrine IV.
Outcomes	Blood loss, side-effects. Blood loss was both estimated visually and measured using alkaline hematin technique
Notes	Third stage management was 'active' using early cord clamping and cord traction

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	High risk	C - Inadequate

Colombia 2002

Methods	Method of random allocation not stated. No placebo use or blinding of outcome assessments
Participants	75 women with vaginal delivery in Colombia. Exclusion criteria: asthma, coagulopathy, twins, stillbirth, lacerations, and "amniotic fluid in the blood collection"
Interventions	Misoprostol 50 mcg sublingually after cord clamp vs oxytocin 16 m IU per minute intravenously after cord clamp vs methylergometrine 0.2 mg after placenta delivery
Outcomes	Blood loss, side-effects, cost. Method of collection or estimation of blood loss not stated.

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Colombia 2002 *(Continued)*

Notes	Management of third stage: no mention of third stage management technique. No reported postrandomization exclusions or loss to follow up. Analysis was based on the total population of 75 women

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Egypt 1993

Methods	Random allocation from a table of random numbers. No mention of blinding or placebo use
Participants	150 low-risk women after vaginal delivery in Assiut, Egypt. Excluded: labour < 2 hours, prolonged labour (> 24 hours), magnesium sulphate therapy during labour, history of postpartum haemorrhage, chorioamnionitis, multiple pregnancy, antepartum haemorrhage and episiotomy
Interventions	Carboprost trometamol* 0.250 mg IM vs methylergometrine maleate 0.2 mg IV
Outcomes	Blood loss, duration of third stage, side-effects. Measurement of blood loss: immediate blood loss was collected in trays and measured. Also, pads were used to collect blood for 4 hours and weighed
Notes	Management of third stage: reported as active but only uterotonic use is mentioned. No mention of exclusions or missing data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Egypt 1997

Methods	Randomization using table of random numbers. No mention of blinding or placebo use
Participants	132 high-risk women after vaginal delivery in Assiut, Egypt. 'High risk' risk factors included: previous history of postpartum haemorrhage, high parity, uterine overdistention due to multiple pregnancy, polyhydramnios or fetal macrosomia, prolonged labour, placental abnormalities or chorioamnionitis Exclusion criteria: organic heart disease, bronchial asthma, epilepsy, renal disease, caesarean section, episiotomy
Interventions	Carboprost trometamol* 250 mcg IM vs methylergonovine maleate 0.4 mg IV, vs oxytocin 10 IU IV

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Egypt 1997 *(Continued)*

Outcomes	Blood loss, duration of third stage. Measurement of blood loss - blood collected in trays and measured. Sterile pads were weighed
Notes	Management of third stage: reported only as active. No report of exclusion after randomization.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

France 2001

Methods	Randomly drawn envelopes containing the treatment codes. Placebos were not used. No placebo use.
Participants	602 women after vaginal delivery in France. Exclusion criteria: preterm birth (< 32 weeks), antepartum haemorrhage, intrauterine fetal death, uterine scar, caesarean section, multiple pregnancy, pre-eclampsia
Interventions	Misoprostol 600 mcg orally vs oxytocin 2.5 IU IV given after cord clamp, vs no uterotonic
Outcomes	Blood loss, duration of third stage, side-effects. Blood loss was measured.
Notes	Management of the third stage: active with immediate cord clamping

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Gambia 2005

Methods	Randomization generated by computer, allocation concealment by sealed, opaque envelopes. Power calculation made. Outcome assessments were blinded
Participants	1229 women delivering vaginally at home by trained birth attendants in rural Gambia
Interventions	Misoprostol 600 mcg orally vs oral ergometrine 2 mg.
Outcomes	Blood loss, postpartum haemoglobin. Blood loss was measured by collection of blood, pads and linen and weighing until 1 hour after delivery

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Gambia 2005 *(Continued)*

Notes	Management of the third stage: controlled cord traction, delayed cord clamping (after cessation of pulsation), early suckling of the breast No loss to follow up.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Ghana 2000

Methods	Randomized, double-blind, controlled trial. Randomization sequence generated by computer. Allocation by sequentially numbered, opaque packets containing active and placebo medications. The packets and misoprostol solution were prepared by a pharmacist not involved in the trial. Power calculation was based on a difference of drop in haemoglobin concentration (> 0.1 g/dl)
Participants	401 women delivering vaginally at the Korle Bu teaching hospital and its clinics in Accra, Ghana. Women were excluded if they were at risk of postpartum haemorrhage (grand multiparae, multiple gestation, gestation < 32 weeks, gestational hypertension with haemolysis-elevated liver enzymes-low platelets syndrome, hydramnios, previous postpartum haemorrhage, coagulation abnormalities, precipitous labour, chorioamnionitis and oxytocin induction or augmentation of labour
Interventions	Misoprostol 400 mcg in powdered form orally (in 50 ml of water) and 1 ml IM injection of normal saline (placebo) vs powdered lactose placebo orally (in 50 ml of water) and 1 ml IM injection of 10 IU oxytocin
Outcomes	Primary outcome: drop in haemoglobin concentration; side-effects Blood loss measurement: clinical estimation.
Notes	Management of third stage: active with cord traction. The authors mention that they report the data as intention to treat although outcome data are missing for 9/401 women

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Ghana 2006

Methods	Random-number scheme generated by computer. Allocation concealment by opening the next sequentially-numbered, sealed, opaque envelope. The study was not blinded. Power calculation is reported
Participants	450 women delivering vaginally at Holy Family hospital, Techiman, Ghana. Women at both high and low risk for PPH were included

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Ghana 2006 *(Continued)*

Interventions	Misoprostol 800 mcg orally vs oxytocin 10 IU IM.
Outcomes	Primary outcome: change in haemoglobin concentration, other measures of blood loss, side-effects. Blood loss was estimated
Notes	Management of the third stage: 'active', no further details. No loss to follow up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Guinea-Bissau 2005

Methods	Random-number list used for randomization scheme. Allocation concealment by sealed, opaque, consecutively-numbered envelopes. Outcome assessments were blinded
Participants	661 women delivering at a primary care centre in Guinea-Bissau
Interventions	Misoprostol 600 mcg sublingual vs identical placebo.
Outcomes	Blood loss, side-effects. Blood loss was measured by collecting blood in swabs and absorbent drape and then weighing them
Notes	Management of the third stage: active with early cord clamping and controlled cord traction. The midwives were trained in these procedures before the start of the trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Holland 1991

Methods	Random allocation was by allocating identical numbered boxes containing trial medications. Method of generation of numbers was not stated. Outcome assessments were not blinded. Saline injections were used as placebo
Participants	74 low-risk women with spontaneous labour and vaginal delivery in Nijmegen and Bergen op Zoom, Holland
Interventions	Sulprostone** 0.5 mg IM vs oxytocin 5 IU IM vs saline.

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Holland 1991 *(Continued)*

Outcomes	Blood loss, duration of third stage, side-effects. Measurement of blood loss: blood and clots collected in trays, swabs and linen weighed for the first hour after delivery
Notes	Management of third stage: 'conservatively', cord clamped within 1 minute, women asked to push after signs of separation, no cord traction or fundal pressure. 3/77 excluded (2 because of induction of labour, 1 vacuum delivery). There were more multiparous women with fewer episiotomies in the sulprostone group despite randomization

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Holland 1995

Methods	Random allocation to pharmacy coded identical boxes containing trial medications. Outcome assessments were blinded. Placebo use
Participants	69 women with a history of previous postpartum blood loss of more than 1000 ml were eligible for this trial conducted in Leiden, Holland. Exclusion criteria: coagulation disorders, anticoagulant treatment, fibroids, multiple pregnancy, hypertension and induction of labour were excluded
Interventions	Sulprostone** 0.5 mg IM at delivery of anterior shoulder + placebo after delivery of placenta vs oxytocin 5 IU IM at delivery of anterior shoulder + methylergometrine 0.2 mg IM after delivery of placenta
Outcomes	Blood loss, duration of third stage, side-effects. Measurement of blood loss: blood and clots were collected in trays and linen weighed
Notes	Management of third stage: fundal pressure while holding lower segment of the uterus after signs of placental detachment. 12/81 (15%) excluded after randomization and before the intervention. No further exclusions after participation in the trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

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Hong Kong 2001

Methods	Random allocation was by sealed, consecutively-numbered, opaque envelopes. Random allocation scheme was generated by computer. Outcome assessments were not blinded. Power calculation was done
Participants	2058 women with singleton pregnancies and vaginal delivery in 3 hospitals in Hong Kong participated in the trial. Women with pre-eclampsia, cardiac disease and asthma, conditions requiring prophylactic oxytocin infusion after delivery (uterine fibroids, grand multiparity) were excluded
Interventions	Misoprostol 600 mcg oral after delivery of the baby, vs oxytocin 5 IU + ergometrine 0.5 mg IM at delivery of anterior shoulder
Outcomes	Blood loss, duration of third stage, delayed haemorrhage, maternal haemoglobin after delivery, side-effects. Shivering was assessed using a visual analogue scale. Blood loss was estimated.
Notes	Management of third stage: controlled cord traction after signs of placental separation No loss to follow up or postrandomization exclusions were reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

India 1988c

Methods	Random allocation by serially numbered, sealed envelopes. There was no placebo use or blinding of outcome assessments
Participants	300 women in 3 centres in India. No mention of risk status. No note of exclusion criteria.
Interventions	PGF2alpha 0.125 mg IM vs methylergometrine 0.2 mg IV.
Outcomes	Blood loss, duration of third stage, side-effects. Measurement of blood loss: blood was collected in trays for 4 hours postpartum and measured
Notes	Management of third stage: no mention of the third stage management technique

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

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India 2001b

Methods	Randomized trial. No further details. Unclear if outcome assessments were blinded
Participants	120 women with at least 1 risk factor for atonic haemorrhage at Jawaharial Institute of Medical Education and Research Hospital in Pondicherry, India
Interventions	Group A: methylergometrine 0.2 mg IV. Group B: oxytocin 10 IU in 10 ml saline into the umbilical cord. Group C: carboprost 0.250 mg IM.
Outcomes	Blood loss, side-effects. Blood loss measurement not mentioned
Notes	Management of third stage: 'active' with controlled cord traction following signs of separation. No loss to follow up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

India 2004b

Methods	Random allocation by sealed, consecutively-numbered envelopes. Unclear if outcome assessments were blinded
Participants	120 low-risk women at a rural health centre in New Delhi, India
Interventions	Misoprostol 400 mcg sublingually vs 0.2 mg methylergometrine IV
Outcomes	Blood loss, side effects. Blood loss was measured collecting all blood and weighing the linen and swabs
Notes	Management of the third stage: active with cord traction.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

India 2005a

Methods	Random allocation, no further details. Unclear if outcome assessments were blinded
Participants	200 primiparous women with singleton deliveries at Lok Nayak Hospital, New Delhi, India
Interventions	Misoprostol 600 mcg orally immediately after delivery vs 0.2 mg methylergometrine IV at delivery of anterior shoulder

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India 2005a *(Continued)*

Outcomes	Blood loss, side-effects. Blood loss measurement method not mentioned
Notes	Management of the third stage: early cord clamping but no mention of placental delivery. No mention of missing data or loss to follow up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

India 2006a

Methods	Randomization by computer-generated random-number list, allocation concealment by opening sealed opaque envelopes. Unclear if outcome assessments were blinded
Participants	100 women undergoing caesarean section at the All India Institute of Medical Sciences, New Delhi, India. Women with risk factors for PPH were not eligible
Interventions	Misoprostol 400 mcg sublingually vs 20 IU oxytocin in 1 litre lactated Ringer's solution at 125 ml/h. All women had spinal anaesthesia
Outcomes	Blood loss, side-effects. Blood loss measurement: Volume of blood in the suction bottle + weighing of blood soaked linen
Notes	Management of the third stage: not applicable.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

India 2006b

Methods	Randomization achieved by computer-generated numbers. No details regarding allocation concealment available
Participants	2023 women delivering at the Christian Medical College Hospital, Vellore, India. Women with cardiac disease, bronchial asthma, rhesus factor incompatibility, pregnancy-induced or pregnancy-aggravated hypertension and caesarean delivery were excluded
Interventions	Misoprostol 400 mcg orally vs oxytocin 10 IU IM versus ergometrine 0.2 mg IV

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India 2006b *(Continued)*

Outcomes	Blood loss, haemoglobin levels, side-effects. Blood loss measurement: large plastic bag placed under the buttocks following drainage of amniotic fluid. The blood was then transferred to a measuring jar
Notes	Management of the third stage: active management.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

India 2006c

Methods	Computer-generated, random-number schedule with a random block list. Random allocation by giving the next of a series of non-distinguishable envelopes containing active or placebo tablets. Identical placebos were used. Outcome assessments were blinded
Participants	1620 women delivering at home or primary care centre in 4 primary health centre areas of Belgaum District, Karnataka State, India. Women were delivered by ANMs who were trained in the trial procedures and the intervention. 2 sets of midwives were involved in the study. 18 at the beginning and 12 leaving and replaced by 7 new ANMs
Interventions	Misoprostol 600 mcg orally vs identical placebos.
Outcomes	Blood loss, side-effects. Blood loss measurement: A calibrated blood collection drape placed under the buttocks following delivery. Blood loss was measured after 1 hour and 2 hours
Notes	Management of the third stage: the ANMs practised expectant management of the third stage of labour apart from the uterotonic in the intervention arm

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

India 2006d

Methods	Randomized study, no further details presented. Unclear if outcome assessments were blinded
Participants	120 low-risk women delivering at the Comprehensive Rural Health Services Project, a rural health centre affiliated with the All India Institute of Medical Sciences, New Delhi, India. Women who received oxytocin during labour, caesarean section delivery, multiple pregnancy and Hb < 8 g/dl were excluded
Interventions	Misoprostol 400 mcg rectally vs PG-F2alpha 125 mcg IM.

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India 2006d *(Continued)*

Outcomes	Blood loss. Blood loss measurement: by clinical estimation.
Notes	Management of the third stage: not mentioned.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Mozambique 2001

Methods	Randomized double-blind trial. Generation of allocation sequence unclear. Double placebos prepared by a pharmacist independent of the trial on a daily basis and provided to the investigators upon request. Outcome assessments were blinded
Participants	663 women with uncomplicated vaginal delivery between 30 and 42 weeks of gestation at Central Hospital of Maputo, Mozambique. Women undergoing induction or augmentation of labour were excluded
Interventions	Misoprostol 400 mcg dissolved in 5 ml saline and administered rectally as a micro-enema + 1 ml saline placebo IM vs oxytocin 10 IU administered IM + 5 ml saline micro-enema (placebo)
Outcomes	Blood loss, side-effects. Blood loss measured by a metal collector placed under the buttocks after delivery until the woman was moved from the delivery room
Notes	Management of third stage not described. 26/350 (7.4%) in the misoprostol group and 11/350 (3.1%) in the oxytocin group were excluded after randomization because of emergency caesarean section or incomplete data collection

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Nigeria 2003

Methods	Randomized double-blind trial with identical looking double placebos. Randomization schedule generated using random-number tables. Allocation concealment achieved by using sealed opaque packets containing both active and the corresponding placebo medication
Participants	496 low-risk women having vaginal deliveries in 2 hospitals in Delta State, Nigeria. Women undergoing caesarean section and who had other risk factors for haemorrhage were excluded

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Nigeria 2003 *(Continued)*

Interventions	Misoprostol 600 mcg in powder form dissolved in 50 ml water per os vs oxytocin 10 IU IM at delivery of anterior shoulder
Outcomes	Blood loss, postdelivery haemoglobin, side-effects. Blood loss estimated by the clinicians
Notes	Management of third stage: controlled cord traction, no other details No loss to follow up or postrandomization exclusions reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Singapore 1995

Methods	Random allocation by a random-number table. Blinding of some outcome assessments
Participants	115 women with spontaneous labour and delivery in Singapore. Exclusion criteria: multiple pregnancy, any antenatal complications
Interventions	Carboprost trometamol* 125 mcg IM vs ergometrine-oxytocin 0.5 mg IM
Outcomes	Blood loss, need for additional uterotonics, transfusion, haemoglobin levels, side-effects. Measurement of blood loss: blood and clots in the first 2 hours after delivery mopped with absorbent paper, sanitary pads collected for the next 22 hours, and then measured
Notes	Management of third stage: controlled cord traction after placenta separation. 3/115 (2.6%) women were excluded after randomization.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

South Africa 1998a

Methods	Random allocation by computer-generated, random sequence for sealed opaque envelopes. No placebo use. Outcome assessments were not blinded
Participants	491 women at low risk for PPH at Natalspruit Hospital, Johannesburg, South Africa. Exclusion criteria: not noted.
Interventions	Misoprostol 400 mcg rectally vs ergometrine-oxytocin 1 ampoule IM

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South Africa 1998a *(Continued)*

Outcomes	Blood loss, duration of third stage, side-effects. Measurement of blood loss: by estimation.
Notes	Loss to follow up was minimal for primary outcomes (2-3%) with the exception of postpartum haemoglobin which was measured in 67% and 65% of women in the misoprostol and ergometrine-oxytocin groups respectively. A small number of women (unspecified) allocated to ergometrine-oxytocin were excluded because of high blood pressure discovered after randomization. However, results were similar to the whole group when all hypertensives were excluded in a subgroup analysis Third stage management was active.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

South Africa 1998b

Methods	Random allocation by computer-generated random sequence. Double-blinded, placebo-controlled trial. Tablets kept in numbered, sealed, opaque containers. Non-identical placebo tablets
Participants	500 women after delivery at Coronation Hospital, Johannesburg, South Africa. No mention of risk status. Exclusion criteria: oxytocin infusion in progress at the time of delivery, hypertension, diabetes, previous caesarean section delivery
Interventions	Misoprostol 400 mcg orally vs placebo.
Outcomes	Blood loss greater than or equal to 1000 ml within first hour of birth, use of additional uterotonics, side-effects, third stage 30 minutes or longer, manual removal of the placenta, blood transfusion. Measurement of blood loss: blood and clots collected in bedpans and volume assessed. Linen weighed
Notes	Management of third stage: placenta removed by cord traction once firm uterine contraction diagnosed by palpation. No withdrawals after randomization.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

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South Africa 1998c

Methods	Random allocation by computer-generated random numbers. Tablets kept in numbered, sealed, opaque containers. Non-identical placebo tablets. Outcome assessments were blinded
Participants	550 low-risk women after delivery at Coronation Hospital Johannesburg, South Africa. Exclusion criteria: not noted.
Interventions	Misoprostol 400 mcg rectally vs placebo.
Outcomes	Blood loss greater than or equal to 1000 ml, use of additional uterotonics, spontaneous delivery of the placenta, third stage longer than or equal to thirty minutes, side-effects. Measurement of blood loss: blood collected in bedpan until 1 hour after delivery. Linens weighed
Notes	Management of third stage: placenta delivered either by cord traction or spontaneous expulsion. Exclusions after randomization: records for 4 allocations (all in placebo group), could not be traced

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

South Africa 1998d

Methods	Random allocation according to a computer-generated random sequence. Serially numbered, opaque test tubes. Outcome assessments were blinded
Participants	600 women after delivery at Coronation Hospital, Johannesburg, South Africa. No mention of whether they are high or low risk. No mention of exclusion criteria
Interventions	Misoprostol 600 mcg orally vs misoprostol 400 mcg orally vs placebo
Outcomes	Shivering, pyrexia. Blood loss was measured using a flat bed pan.
Notes	Management of third stage: placenta removed by cord traction after firm contraction of uterus. No exclusions after randomization.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

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South Africa 2001

Methods	Random allocation according to a computer-generated random sequence. Serially numbered, opaque test tubes. Outcome assessments were blinded
Participants	600 women after delivery at Coronation Hospital, Johannesburg, South Africa. Exclusion criteria: no mention of exclusion criteria.
Interventions	Misoprostol 600 mcg oral vs placebo.
Outcomes	Shivering, pyrexia. Measurement of blood loss: blood in bed pan measured, linen and sanitary towels weighed
Notes	Management of third stage: placenta removed by cord traction after firm contraction of uterus. No exclusions after randomization.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Switzerland 1999

Methods	Random allocation using random-number tables. Trial was double blinded
Participants	65 low-risk women with vaginal deliveries at Basel University Hospital, Basel, Switzerland. Exclusion criteria: multiple pregnancy, pre-eclampsia, previous PPH or antepartum haemorrhage, caesarean delivery
Interventions	Misoprostol 600 mcg orally vs placebo.
Outcomes	Blood loss, length of third stage, use of additional uterotonics, side-effects, haematocrit values. Measurement of blood loss: estimation by delivery physicians
Notes	Management of third stage: early cord clamping and cord traction. No exclusions after randomization.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

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Turkey 2002

Methods	Randomization based on computer-generated random numbers. Sealed, consecutively-numbered, opaque envelopes were used. Identical placebos were used except for the misoprostol tablets which were similar in size and colour but not in shape. There was blinding of outcome assessments. Midwives administered the misoprostol tablets, but residents that were blinded to the intervention, did the outcome assessments
Participants	1633 women with vaginal deliveries in Ankara, Turkey. Exclusion criteria: Gestational age < 32 wks, caesarean delivery, hypersensitivity to prostaglandins
Interventions	Women randomized into 4 groups, all received corresponding placebos. Group 1: oxytocin 10 IU IV plus misoprostol 400 mcg rectally after cord clamp, followed by 2 doses 4 and 8 hours after delivery of 100 mcg misoprostol. Group 2: misoprostol 400 mcg rectally after cord clamp followed by 2 doses 4 hours apart of 100 mcg misoprostol. Group 3: oxytocin 10 IU IV. Group 4: oxytocin 10 IU IV plus 1 ml methylergometrine IM.
Outcomes	Blood loss, transfusion, change in Hgb, need for additional uterotonics, length of the third stage, subsequent evacuation of uterus, frequency of delayed haemorrhage, side-effects. Clinical estimation of blood loss was done
Notes	Active management of third stage with early cord clamping, traction, and uterine massage. 27 exclusions after randomization secondary to lack of Hgb measurements. These were spread out among the 4 groups. Concurrent study at this institution with similar design but evaluating oral misoprostol also published and is included in this meta-analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Turkey 2003

Methods	Randomization based on computer generated random numbers. Sealed, consecutively numbered, opaque envelopes were used. Identical placebos were used except for the misoprostol tablets which were similar in size and color but not in shape. There was blinding of outcome assessments. Midwives administered the misoprostol tablets, but residents that were blinded to the intervention, did the outcome assessments
Participants	1800 women with vaginal deliveries in Ankara, Turkey. Exclusion criteria: Gestational age < 32 wks, caesarean delivery, hypersensitivity to prostaglandins
Interventions	Women randomized into 4 groups, all received corresponding placebos. Group 1: oxytocin 10 IU IV plus misoprostol 400 mcg orally after cord clamp, followed by 2 doses 4 and 8 hours after delivery of 100 mcg misoprostol. Group 2: misoprostol 400 mcg orally after cord clamp followed by 2 doses 4 hours apart of 100 mcg misoprostol. Group 3: oxytocin 10 IU IV. Group 4: oxytocin 10 IU IV plus 1 ml methylergometrine IM.

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Turkey 2003 *(Continued)*

Outcomes	Blood loss, transfusion, change in Hgb, need for additional uterotonics, length of the third stage, subsequent evacuation of uterus, frequency of delayed haemorrhage, side effects. Clinical estimation of blood loss was done
Notes	Active management of third stage with early cord clamping, traction, and uterine massage. 226 (12.6%) exclusions after randomization secondary to lack of haemoglobin measurements. Concurrent study at this institution with similar design but evaluating oral misoprostol also published and is included in this meta-analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

United Kingdom 1994

Methods	Method of random allocation not stated. Sealed opaque envelopes used for allocation concealment. Interventions prepared by someone not involved in the study, outside the intervention area (operating theatre) . Outcome assessments were blinded
Participants	60 low-risk women undergoing elective caesarean section in an academic hospital in Oxford, UK. Exclusion criteria: hypertensive disease, asthma, heart disease
Interventions	Prostaglandin group: 15-methyl prostaglandin F2alpha, 125 mcg intramyometrial + placebo. Oxytocin group: 5 IU oxytocin IV bolus injection followed by 15 IU in 500 ml of Ringer's lactate solution + placebo. Both interventions were started after delivery of the baby but before delivery of the placenta
Outcomes	Blood loss, use of additional uterotonics, blood transfusion, side-effects, change in haemoglobin (subset of patients). Measurement of blood loss: clinical estimation.
Notes	Management of third stage: not applicable. No losses to follow up or postrandomization exclusions reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

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United Kingdom 2000

Methods	Random allocation by sealed, opaque, consecutively-numbered envelopes. No blinding of outcome assessments
Participants	1000 women delivering vaginally, in London, UK. Women with a history of asthma, planned caesarean section and water birth were excluded
Interventions	Misoprostol group: 500 mcg misoprostol orally after baby delivered and cord clamped Uterotonic group: this group was given uterotonics at delivery of anterior shoulder. The choice of uterotonics varied according to the hospital policy for different groups of women. Women at high risk of haemorrhage received ergometrine (2%), those with hypertension received oxytocin (18%). All others received ergometrine-oxytocin (80%)
Outcomes	Blood loss, side-effects. Measurement of blood loss: clinical estimation by the midwives
Notes	Management of third stage: 'active': cord traction with signs of separation, oxytocics at anterior shoulder delivery. No mention of postrandomization exclusions or protocol violations

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

United Kingdom 2001b

Methods	Random allocation schedule generated by computer. Allocation made by opening sealed opaque envelopes which contained the names of the groups. No mention of consecutive numbering and opening. The obstetrician, surgical assistant, scrub nurse and recovery midwives were blinded to the group while anaesthetist was not. Double, nonidentical placebos were used
Participants	40 women undergoing elective or emergency caesarean section in a university hospital in London, United Kingdom. Women with 2 or more caesarean sections or a history of previous ruptured uterus were excluded. Other eligibility criteria are not mentioned
Interventions	Misoprostol 500 mcg orally + 2 ml IV normal saline bolus vs 10 IU oxytocin bolus + 2 placebo tablets
Outcomes	Blood loss (clinical estimation), change in Hgb levels, shivering (assessed in the recovery room), temperature within 1 hour
Notes	Management of third stage: 'active' during caesarean section. No withdrawals after caesarean section.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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United Kingdom 2001b *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

United Kingdom 2003

Methods	Random allocation prepared by independent statistician using computer-generated random numbers with blocked randomization. Sequentially numbered, sealed, opaque, envelopes used. No placebos used. No blinding of outcome assessments
Participants	275 women with vaginal delivery in London, UK. Exclusion criteria: < 37 wks gestation, < 18 yrs old, multiple gestation, induced labour, asthma, cardiac, renal or hepatic disorder. Study was reported in conjunction with a misoprostol pharmacokinetics trial
Interventions	Misoprostol 600 mcg orally vs 600 mcg rectally vs 400 mcg rectally
Outcomes	Side-effects, clinical estimation of blood loss, duration of third stage, manual removal of placenta
Notes	"Usual" management of third stage with cord traction. No losses to follow up or postrandomization exclusions. Blood loss estimated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

USA 1990

Methods	Method of random allocation not stated. Double-blinded trial
Participants	46 women at low risk for postpartum haemorrhage undergoing delivery by caesarean section in Arkansas, USA. Exclusion criteria: hypertension, asthma, pre-eclampsia, chorioamnionitis, multiple gestation or were receiving tocolytic agents
Interventions	Carboprost tromethamine* 0.125 mg intramyometrial vs oxytocin 20 IU intramyometrial. Both groups received 20 IU of oxytocin in 1 litre saline after delivery
Outcomes	Haematocrit change after delivery, blood loss not measured.
Notes	Management of third stage: not applicable. No losses to follow up.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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USA 1990 *(Continued)*

Allocation concealment?	Low risk	A - Adequate

USA 2001

Methods	Random allocation sequence concealed until enrolment. Packs containing both active and placebo were made available after random allocation. It is not clear if the placebos are identical. No mention of blind outcome assessments
Participants	400 women in active labour or undergoing induction of labour in Los Angeles, USA were enrolled. Women with multiple gestation, known coagulation disorders, contraindication to prostaglandin or oxytocin use, known initial haemoglobin below 7.0 mg/dl and an indication for caesarean section were excluded
Interventions	Misoprostol 400 mcg rectally + placebo (2 ml saline) vs oxytocin 20 IU + placebo (lactose tablets). Oxytocin (and its placebo) was administered as IV infusion in 1 L of Ringer's lactate solution
Outcomes	Blood loss (estimated and measured by weighing linen etc.), haematocrit, side-effects
Notes	Management of the third stage not mentioned. Exclusions after randomization: 75/400 (18.75%), 73 had caesarean section during labour, one had Hb < 7.0 mg/dl and one was discharged home before delivery

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

USA 2004

Methods	Random allocation sequence generated by using a table of random numbers. Active and placebo (similar but not identical) were placed in opaque, numbered vials. Power calculation was made. Outcome assessments were not blinded
Participants	756 women with anticipated vaginal delivery at a maternity hospital in Florida, USA
Interventions	Misoprostol 200 mcg buccal vs placebo. All women received intravenous infusion of 20 IU oxytocin in 1 litre of saline at 10 ml/min for 30 minutes (i.e. received approximately 6 IU oxytocin IV)
Outcomes	Blood loss, haemoglobin measurements, side-effects. Blood loss was estimated by the attending physician.
Notes	Management of the third stage: active management with early cord clamping. controlled cord traction and oxytocin after delivery of the placenta 756/848 eligible women were randomized. Analysis by intention to treat

Risk of bias

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USA 2004 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

USA 2005

Methods	Randomized, placebo-controlled. No mention of random-number generation scheme. Allocation concealment by pharmacy-assigned numbers to opaque vials containing either misoprostol tablets or oxytocin ampoules. Outcome assessments were blinded
Participants	352 women undergoing caesarean section in Orlando, Florida, USA
Interventions	Misoprostol 200 mcg buccal vs placebo at cord clamping. All women received 20 IU IV oxytocin in 1000 ml saline
Outcomes	Blood loss, additional uterotonics. Blood loss was estimated following 'standard' procedures.
Notes	No loss to follow up.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

WHO 1999

Methods	Random allocation sequence, generated centrally. Sealed and numbered identical treatment packs taken consecutively from a dispenser. Double-blinded, placebo controlled pilot trial
Participants	597 women after delivery in Khon Kaen, Thailand and Johannesburg, South Africa. Risk status not stated Exclusion criteria: asthma, other severe chronic allergic condition, if delivery considered an abortion, planned caesarean section, not willing or able to give informed consent
Interventions	Misoprostol 600 mcg orally vs misoprostol 400 mcg orally vs oxytocin 10 IU IV
Outcomes	Shivering, pyrexia, side-effects, blood loss from delivery to transferral of mother to postnatal care Measurement of blood loss: collected blood poured in standard measuring jar. Linen not weighed. Small gauze swabs soaked with blood put into measuring jar and included in measurement
Notes	Management of third stage: uterotonics, clamping and cutting of cord immediately after delivery, fundal or suprapubic pressure with cord traction after signs of placental separation. Exclusion after randomization: 8 women in the oxytocin group did not comply with treatment (6 had an emergency caesarean section, 1 was HIV positive and mistakenly excluded, 1 whose ampoule was not located). One woman in the 600 mcg group was excluded because her tablets could not be located, and one woman in the 400 mcg group was excluded because of an emergency caesarean section

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WHO 1999 *(Continued)*

Risk of bias	

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

WHO 2001

Methods	Random allocation sequence, generated centrally. Sequentially-numbered, identical treatment packs drawn from a treatment pack dispenser. Double blinding achieved by use of double placebos
Participants	18,530 women expecting vaginal delivery in 9 countries. Countries were Argentina, China, Egypt, Ireland, Nigeria, South Africa, Switzerland, Thailand, and Vietnam. Exclusion criteria: pyrexia (> 38 degrees C) on admission to labour ward, severe asthma, bleeding disorders, elective caesarean section, no consent
Interventions	Misoprostol 600 mcg orally + placebo IV/IM, vs oxytocin 10 IU IV/IM + placebo tablets
Outcomes	Blood loss, shivering, pyrexia, nausea, vomiting, diarrhoea, need for transfusion, manual removal of placenta, exploration under general anaesthesia, hysterectomy, admission to ICU, maternal deaths. Measurement of blood loss: collected blood poured in standard measuring jar. Small gauze swabs soaked with blood put into measuring jar and included in measurement. Linen weighed in some centres
Notes	Management of third stage: uterotonics, clamping and cutting of cord immediately after delivery, fundal or suprapubic pressure with cord traction after signs of placental separation. 50/9264 (0.54%) excluded after randomization in the misoprostol group, 37 because of an emergency caesarean section, and 13 for loss to follow up. 38/9226 (0.41%) excluded after randomization in the oxytocin group, 34 for emergency caesarean section and 4 lost to follow up

Risk of bias	

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Zimbabwe 2001

Methods	Random allocation sequence generated by computer, allocation by numbered, sealed, opaque envelopes. Placebos used but were not identical. It is not mentioned whether outcome assessments were blinded or not
Participants	500 low-risk women delivering at Harare Maternity Hospital, Zimbabwe were included. Women with a history of PPH, disseminated intravascular coagulation, antepartum haemorrhage, coagulation disorders, operative delivery, multiple pregnancy, history of asthma and known allergies to misoprostol or oxytocin were excluded

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Zimbabwe 2001 *(Continued)*

Interventions	Misoprostol 400 mcg orally + 1 ml saline (placebo) vs oxytocin 10 IU IM + 2 placebo tablets
Outcomes	Blood loss, side-effects. Measurement of blood loss: Blood volume in jug + weighing of soiled linen
Notes	Management of the third stage not described. Exclusions after randomization: one women excluded because of undiagnosed twin delivery

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

* (15(S) 15 methyl PGF2alpha)
** Synthetic PGE2 derivative (16-phenoxy-17,18,19,20-tetranor-PGE2-methylsulphonamide)
ANM: auxiliary nurse midwives
Hgb: haemoglobin
ICU: intensive care unit
IM: intramuscular(ly)
IU: international unit(s)
IV: intravenous(ly)
PPH: postpartum haemorrhage
vs: versus
wks: weeks

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

Study	Reason for exclusion
Austria 1983	No clinically relevant outcomes reported. Healthy women delivering at term who had a normal duration of labour (< 12 hours) and without the use of oxytocics before delivery were recruited. Immediately following the separation of the placenta, a twin catheter was introduced into the cavity for intrauterine pressure measurement which was recorded on the cardiotocograph. The women were randomized to receive methergin (methylergometrine) 0.2 mg, or oxytocin 2 IU, or sulprostone 0.5 mg or saline, all administered intramuscularly. Sulprostone had the quickest onset of action and strongest increase in uterine contractility whereas methergin had the longest duration of action on uterine contractility
Canada 2004	Not a randomized controlled trial. A nested study within a randomised controlled trial to look at peripheral blood flow and temperature changes in women receiving misoprostol or oxytocin
China 1997	This trial was reported as randomized but no details of the method of randomization were given. The two study groups were not balanced (260 versus 100), and they were further randomized into subgroups

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(*Continued*)

China 1998	Randomized controlled trial of misoprostol versus oxytocin in caesarean section deliveries only. Data are not presented in a form that can be extracted for the meta-analysis
China 1998b	This trial randomized 80 women to 1 mg carboprost methylate intravaginally versus sublingually vs ergometrine IV. The data were not in a form suitable for extraction for this meta-analysis
China 2001	This trial randomized 348 women into 4 groups of misoprostol 200, 400, and 600 micrograms orally, and oxytocin 20 units intramuscularly. Data were presented only in means, and were not presented in a form suitable for extraction and inclusion in this meta-analysis
China 2004b	Randomized, double blind trial of 298 low-risk women delivering vaginally in Hong Kong, China. Oral misoprostol vs IV oxytocin. The trial is excluded because the number of women in each group are not described and the report is available as an abstract. The authors have not responded to the request for additional information and clarification. There was no statistically significant difference in blood loss > 500 and 1000 ml. Additional oxytocics were used in 25.2 vs 7.5% in the misoprostol and oxytocin groups respectively
China 2004c	Data are not in a usable format. RCT comparing misoprostol 400 mcg + syntometrine vs syntometrine. The author contacted but no response
Egypt 1999	140 women were allocated to receive either 2 different doses of rectal misoprostol or 5 units of oxytocin and 0.2 mg ergometrine intramuscularly. There is no indication of any randomized comparison between the groups
Hungary 1979	The reason for exclusion is that the data are not presented in a usable form. The study is a randomized comparison of 1 mg intramyometrial prostaglandin F2alpha (47 women), 0.2 mg intravenous ergometrine (50) and no treatment (43). Prostaglandin F2alpha reduced the blood loss in the third stage of labour significantly when compared with ergometrine and no treatment
India 1988a	60 women were allocated to 125 microgram PGF2alpha intramuscularly or no uterotonic. There is no indication of any randomized comparison between the 2 groups
India 1988b	Multicentre study carried out in 4 centres. Of these, 2 employed a random allocation scheme and 2 used a sequential scheme. The reason for exclusion is that the results are presented together and it is not possible to extract data for those utilising random allocation
India 2000a	There are no data that can be extracted to evaluate the validity of the methods used and the outcome data in this study from the conference abstract. When the study is published in full it will be evaluated again
India 2000b	There are no data that can be extracted to evaluate the validity of the methods used and the outcome data in this study from the conference abstract. When the study is published in full it will be evaluated again
India 2000c	There are no data that can be extracted to evaluate the validity of the methods used and the outcome data in this study from the conference abstract. When the study is published in full it will be evaluated again
India 2001a	This study is reported as randomized double blind but there is no mention of placebos. There is also a discrepancy in the results between the text and the tables. 200 women were assigned either misoprostol orally 400 mcg or methylergometrine

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(*Continued*)

India 2005b	The study is reported as a RCT comparing carboprost with methylergometrine but the results are analysed by risk subgroups only and they are imbalanced between the two random allocation groups
India 2006e	This is a randomized trial (cluster) of an educational intervention to implement active management of the third stage of labour using misoprostol. The control group received standard practice which was 'no special training' and no use of misoprostol
Indonesia 2002	Data to evaluate the validity of the methods used are not available in this published abstract. When the study is published in full it will be evaluated again. This study involves 196 women undergoing full term vaginal delivery. 98 women were randomly allocated to 600 micrograms of oral misoprostol or 10 IU of oxytocin intramuscularly immediately after the baby was born. The length of the third stage of labour was 8.122 minutes for the misoprostol group and 8.388 minutes for the oxytocin group. Third stage blood loss for the misoprostol and oxytocin group was respectively 144.286 ml and 131.020 ml. Shivering occurred in 13.3% in the misoprostol group and 2.0% in the oxytocin group
Israel 1992	This is a randomized controlled trial comparing intraumbilical PGF2alpha with saline injection. Although a prostaglandin was used for the management of the third stage of labour the mechanism of action may not be comparable to other routes of administration. This paper will be considered for inclusion in another review on the management of the third stage (intraumbilical uterotonics)
Italy 1988	Data from this trial were published in an abstract. It is excluded because no full publication of the trial data could be located
Japan 1976	There does not seem to be a randomized comparison between study groups. 4 prostaglandin groups were studied: a. systemic: a.1. intramuscular (gluteal), a.2. continuous intravenous drip infusion, b. local: b.1. transabdominal intramyometrial injection, b.2. transvaginal intramyometrial injection. These groups were compared to ergot alkaloids. Number of participants are also not balanced (46 in prostaglandin vs 13 in ergot group)
Singapore 1990	The outcome examined in this trial was serum prostaglandin levels
Singapore 2001	This trial has 57 women randomly assigned to receive oral misoprostol 200, 400, 500, 600, or 800 micrograms or ergometrine-oxytocin. Uterine activity was the main outcome, but side-effects were also reported. The data are incomplete and not in a suitable form for extraction
South Africa 1999	Data from this trial were published in an abstract. It is excluded because no further publication of complete trial data was located. This trial evaluates treatment of primary postpartum haemorrhage
Turkey 2005	Randomized, placebo-controlled trial comparing 400 mcg rectal vs 400 mcg vaginal misoprostol vs placebo after delivery of the placenta. Women with haemorrhage were excluded from the analysis after randomization. Authors contacted for clarification
United Kingdom 2001a	Randomized controlled trial of 400 mcg oral misoprostol versus 10 IU IV oxytocin. Primary outcome was 'intraoperative blood loss', which is not one of the outcomes for this review
USA 1983	75 women were randomized to 3e groups of different doses of prostaglandin F2alpha (62.5, 125, 250 microgram intramuscularly). Then another 15 women were sequentially allocated to the same treatment

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(*Continued*)

	groups, in groups of 5. The randomized and non-randomized groups have been reported together in the paper to increase the sample size. It is not possible to extract data on the randomized women alone
USA 1999	Data from this trial were published in an abstract. It is excluded because no further publication of the completed trial data was located and the data presented in the abstract is incomplete

IU: international unit
IV: intravenous
vs: versus

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DATA AND ANALYSES

Comparison 1. Any misoprostol versus no uterotonic/placebo (primary outcomes only)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Severe postpartum haemorrhage (>= 1000 ml)	10		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Oral 600 mcg	5		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2 Oral 400 mcg	2		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.4 Rectal 400 mcg	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.5 Sublingual 600 mcg	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.7 Oral misoprostol 400 mcg + oxytocin versus oxytocin	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.8 Rectal misoprostol 400 mcg + oxytocin versus oxytocin	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Use of additional uterotonics	9		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Oral 600 mcg	4		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2 Oral 400 mcg	2		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.4 Rectal 400 mcg	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.5 Sublingual 600 mcg	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.9 Buccal 200 mcg + oxytocin versus placebo + oxytocin	2		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 2. Oral misoprostol versus no uterotonic/placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal death	2	2849	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.24, 8.81]
1.1 600 mcg	2	2849	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.24, 8.81]
2 Maternal death or severe morbidity	2	2848	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.36, 3.80]
2.1 600 mcg	2	2848	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.36, 3.80]
3 Severe postpartum haemorrhage (>= 1000 ml)	6		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 600 mcg	5		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.2 400 mcg	2		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Postpartum haemorrhage (>= 500 ml)	4		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 600 mcg	4		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2 400 mcg	0		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Blood loss (ml)	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 600 mcg	3		Mean Difference (IV, Fixed, 95% CI)	Not estimable
5.2 400 mcg	0		Mean Difference (IV, Fixed, 95% CI)	Not estimable

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6 Use of additional uterotonics	5		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 600 mcg	4		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2 400 mcg	2		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Blood transfusion	4	3519	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.10, 0.94]
7.1 600 mcg	3	2619	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.06, 0.94]
7.2 400 mcg	2	900	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.08, 4.52]
8 Manual removal of placenta	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 600 mcg	2	1000	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.30, 5.93]
8.2 400 mcg	2	900	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.06, 2.89]
9 Duration of third stage (minutes)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 600 mcg	1	65	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-3.64, 1.64]
9.2 400 mcg	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
10 Third stage >= 30 minutes	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 600 mcg	2	999	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [0.61, 5.34]
10.2 400 mcg	2	900	Risk Ratio (M-H, Fixed, 95% CI)	2.25 [0.70, 7.26]
11 Any side-effect	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.2 400 mcg	1	500	Risk Ratio (M-H, Fixed, 95% CI)	2.08 [1.35, 3.20]
12 Nausea	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
12.1 600 mcg	3		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.2 400 mcg	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13 Vomiting	4		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
13.1 600 mcg	4		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13.2 400 mcg	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14 Headache	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 600 mcg	2	998	Risk Ratio (M-H, Fixed, 95% CI)	2.2 [0.50, 9.77]
14.2 400 mcg	1	398	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.24, 103.49]
15 Abdominal pain	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
15.1 600 mcg	2		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15.2 400 mcg	2		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16 Diarrhoea	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 600 mcg	3	2227	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.34, 2.72]
16.2 400 mcg	1	398	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
17 Any shivering	7		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
17.1 600 mcg	6		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
17.2 400 mcg	2		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18 Severe shivering	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
19 Pyrexia (>= 38 degrees C)	4	3424	Risk Ratio (M-H, Fixed, 95% CI)	6.40 [4.47, 9.18]
19.1 600 mcg	4	3024	Risk Ratio (M-H, Fixed, 95% CI)	6.55 [4.43, 9.67]
19.2 400 mcg	1	400	Risk Ratio (M-H, Fixed, 95% CI)	5.6 [2.21, 14.21]

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Comparison 3. Oral misoprostol versus injectable uterotonics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal death	4	20199	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.14, 7.10]
1.1 800 mcg	1	450	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2 600 mcg	2	18829	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.14, 7.10]
1.3 400 mcg	2	920	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Severe postpartum haemorrhage (>= 1000 ml)	15	29042	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [1.16, 1.51]
2.1 800 mcg	1	450	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2 600 mcg	6	21977	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [1.17, 1.58]
2.3 500 mcg	2	1040	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.43, 1.98]
2.4 400 mcg	7	5575	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.85, 1.74]
3 Postpartum haemorrhage (>= 500 ml)	15		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 800 mcg	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.2 600 mcg	7		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.3 500 mcg	2		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.4 400 mcg	6		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Blood loss (ml)	6		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 600 mcg	3		Mean Difference (IV, Fixed, 95% CI)	Not estimable
4.2 400 mcg	4		Mean Difference (IV, Fixed, 95% CI)	Not estimable
5 Use of additional uterotonics	14		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 800 mcg	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.2 600 mcg	6		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.3 500 mcg	2		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.4 400 mcg	6		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Blood transfusion	14	27858	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.64, 1.02]
6.1 800 mcg	1	443	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.05, 5.45]
6.2 600 mcg	5	21600	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.59, 1.02]
6.3 500 mcg	2	1040	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.34, 1.95]
6.4 400 mcg	7	4775	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.56, 1.77]
7 Postpartum haemoglobin	1	450	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.23, 0.43]
7.1 800 mcg	1	450	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.23, 0.43]
8 Haematocrit drop 10% or more	1	585	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.47, 2.52]
8.1 400 mcg	1	585	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.47, 2.52]
9 Haemoglobin drop 30 mg/L or more	1	585	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.69, 1.88]
9.1 400 mcg	1	585	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.69, 1.88]
10 Manual removal of placenta	12		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 800 mcg	1	450	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.2 600 mcg	6	21806	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.81, 1.16]
10.3 500 mcg	1	1000	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.34, 1.57]
10.4 400 mcg	5	1890	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.58, 1.46]
11 Duration of third stage (minutes)	6		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11.1 600 mcg	2		Mean Difference (IV, Fixed, 95% CI)	Not estimable
11.2 400 mcg	5		Mean Difference (IV, Fixed, 95% CI)	Not estimable
12 Third stage >= 30 minutes	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 600 mcg	4	2954	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.53, 1.89]

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12.2 500 mcg	1	1000	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.44, 1.95]
12.3 400 mcg	2	1271	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.30, 5.99]
13 Any side-effect	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13.2 500 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13.3 400 mcg	1	499	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [1.16, 1.77]
14 Nausea	11		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
14.1 800 mcg	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14.2 600 mcg	6		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14.3 500 mcg	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14.4 400 mcg	4		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15 Vomiting	14		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
15.1 800 mcg	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15.2 600 mcg	7		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15.3 500 mcg	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15.4 400 mcg	6		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16 Diarrhoea	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 800 mcg	1	439	Risk Ratio (M-H, Fixed, 95% CI)	10.85 [0.60, 195.06]
16.2 600 mcg	5	20326	Risk Ratio (M-H, Fixed, 95% CI)	2.52 [1.60, 3.98]
16.3 500 mcg	1	846	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.55, 2.19]
16.4 400 mcg	6	4181	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.67, 2.22]
17 Headache	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 600 mcg	2	2239	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.74, 1.28]
17.2 500 mcg	1	846	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.38, 0.75]
17.4 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18 Any shivering	16		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
18.1 800 mcg	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18.2 600 mcg	7		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18.3 500 mcg	2		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18.4 400 mcg	7		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
19 Severe shivering	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 600 mcg	3	19038	Risk Ratio (M-H, Fixed, 95% CI)	7.28 [4.71, 11.24]
19.2 500 mcg	1	40	Risk Ratio (M-H, Fixed, 95% CI)	9.0 [0.52, 156.91]
19.3 400 mcg	2	1745	Risk Ratio (M-H, Fixed, 95% CI)	4.23 [0.20, 87.88]
20 Pyrexia (>= 38 degrees C)	11		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
20.1 600 mcg	7		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
20.2 500 mcg	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
20.3 400 mcg	4		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 4. Rectal misoprostol versus no uterotonic/placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal death	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Postpartum haemorrhage (>= 500 ml)	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

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3 Severe postpartum haemorrhage (>= 1000 ml)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.2 400 mcg	1	542	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.35, 1.37]
4 Blood loss (ml)	0		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 600 mcg	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
4.2 400 mcg	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
5 Use of additional uterotonics	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.2 400 mcg	1	546	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.31, 1.62]
6 Blood transfusion	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Manual removal of placenta	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.2 400 mcg	1	546	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [0.12, 74.40]
8 Duration of third stage (minutes)	0		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 600 mcg	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
8.2 400 mcg	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
9 Third stage >= 30 minutes	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.2 400 mcg	1	540	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.05, 5.56]
10 Any side-effect	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11 Nausea	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12 Vomiting	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.2 400 mcg	1	546	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.06, 16.14]
13 Headache	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14 Abdominal pain	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14.2 400 mcg	1	546	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [0.12, 74.40]
15 Diarrhoea	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15.2 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16 Any shivering	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16.2 400 mcg	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.03, 2.25]
17 Severe shivering	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
17.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18 Pyrexia (>= 38 degrees C)	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

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Comparison 5. Rectal misoprostol versus injectable uterotonics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal death	1	803	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2 400 mcg	1	803	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Postpartum haemorrhage (>= 500 ml)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2 400 mcg	4	2244	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.92, 1.43]
3 Severe postpartum haemorrhage (>= 1000 ml)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.2 400 mcg	3	1780	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.70, 1.85]
4 Blood loss (ml)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 600 mcg	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
4.2 400 mcg	2	1126	Mean Difference (IV, Fixed, 95% CI)	1.77 [-10.07, 13.60]
5 Use of additional uterotonics	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.2 400 mcg	3	1210	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.16, 2.31]
6 Blood transfusion	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2 400 mcg	4	2013	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.52, 2.04]
7 Manual removal of placenta	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.2 400 mcg	1	223	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.02, 1.40]
8 Duration of third stage (minutes)	3	1941	Mean Difference (IV, Fixed, 95% CI)	0.25 [-0.08, 0.58]
8.1 600 mcg	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
8.2 400 mcg	3	1941	Mean Difference (IV, Fixed, 95% CI)	0.25 [-0.08, 0.58]
9 Third stage >= 30 minutes	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.2 400 mcg	1	803	Risk Ratio (M-H, Fixed, 95% CI)	6.17 [1.39, 27.38]
10 Any side-effect	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11 Nausea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.2 400 mcg	1	215	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [0.57, 4.96]
12 Vomiting	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.2 400 mcg	3	1678	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.57, 3.86]
13 Headache	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13.2 400 mcg	1	215	Risk Ratio (M-H, Fixed, 95% CI)	2.36 [0.75, 7.42]
14 Abdominal pain	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14.2 400 mcg	1	215	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.46, 2.02]
15 Diarrhoea	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15.2 400 mcg	2	1464	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.46, 2.31]

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16 Any shivering	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16.2 400 mcg	4	2003	Risk Ratio (M-H, Fixed, 95% CI)	2.37 [1.89, 2.98]
17 Severe shivering	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
17.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18 Pyrexia (>= 38 degrees C)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18.2 400 mcg	2	1022	Risk Ratio (M-H, Fixed, 95% CI)	2.08 [1.21, 3.57]

Comparison 6. Rectal misoprostol versus intramuscular prostaglandin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal death	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Postpartum haemorrhage (>= 500 ml)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2 400 mcg	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.31, 5.70]
3 Severe postpartum haemorrhage (>= 1000 ml)	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Blood loss (ml)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 600 mcg	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
4.2 400 mcg	1	120	Mean Difference (IV, Fixed, 95% CI)	40.0 [-19.66, 99.66]
5 Use of additional uterotonics	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.2 400 mcg	1	120	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [1.14, 21.86]
6 Blood transfusion	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Manual removal of placenta	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8 Duration of third stage (minutes)	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
8.1 600 mcg	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
8.2 400 mcg	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
9 Third stage >= 30 minutes	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10 Any side-effect	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11 Nausea	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

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12 Vomiting	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13 Headache	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14 Abdominal pain	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15 Diarrhoea	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16 Any shivering	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
17 Severe shivering	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
17.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18 Pyrexia (>= 38 degrees C)	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 7. Sublingual misoprostol versus no uterotonic/placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal death	1	661	Risk Ratio (M-H, Fixed, 95% CI)	3.01 [0.12, 73.60]
2 Severe postpartum haemorrhage (>= 1000 ml)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 600 mcg	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2 400 mcg	0		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Postpartum haemorrhage (>= 500 ml)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 600 mcg	1	661	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.76, 1.04]
3.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Blood loss (ml)	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
4.1 600 mcg	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
4.2 400 mcg	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
5 Use of additional uterotonics	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Blood transfusion	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Manual removal of placenta	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8 Duration of third stage (minutes)	0		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 600 mcg	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable

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8.2 400 mcg	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
9 Third stage >= 30 minutes	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10 Any side-effect	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11 Nausea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 600 mcg	1	661	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.09, 2.72]
11.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12 Vomiting	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 600 mcg	1	661	Risk Ratio (M-H, Fixed, 95% CI)	2.51 [0.79, 7.92]
12.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13 Headache	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14 Abdominal pain	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15 Diarrhoea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 600 mcg	1	661	Risk Ratio (M-H, Fixed, 95% CI)	2.51 [0.79, 7.92]
15.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16 Any shivering	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 600 mcg	1	661	Risk Ratio (M-H, Fixed, 95% CI)	2.43 [1.96, 3.01]
16.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
17 Severe shivering	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
17.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18 Pyrexia (>= 38 degrees C)	1	661	Risk Ratio (M-H, Fixed, 95% CI)	7.11 [3.85, 13.12]
18.1 600 mcg	1	661	Risk Ratio (M-H, Fixed, 95% CI)	7.11 [3.85, 13.12]
18.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 8. Sublingual misoprostol versus injectable uterotonic

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal death	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Severe postpartum haemorrhage (>= 1000 ml)	3	270	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.23, 1.27]
2.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2 400 mcg	2	220	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.24, 1.53]
2.3 50 mcg	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 2.99]
3 Postpartum haemorrhage (>= 500 ml)	4	330	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.90, 1.27]
3.1 600 mcg	1	60	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.40, 10.11]
3.2 400 mcg	2	220	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.94, 1.21]
3.3 50 mcg	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.37, 2.05]
4 Blood loss (ml)	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 600 mcg	0		Mean Difference (IV, Fixed, 95% CI)	Not estimable

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Medical treatment of postpartum haemorrhage

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Abstract
Postpartum haemorrhage (PPH) may occur unexpectedly in any woman who has given birth. All birth attendants must have the skills and knowledge to manage PPH quickly and effectively. This may include rubbing up the uterus and bimanual compression, resuscitation, removal of retained placental tissue and surgical procedures.

The use of drugs to contract the uterus, and to enhance coagulation, are one element in the holistic management. The following sequence of drugs may be used:

Used by midwife:
1. If not recently given as prophylaxis and drip not yet up, oxytocin 10u im
2. Iv infusion oxytocin 20u in 1000ml Ringers lactate or saline at 120-240 mL/hour
3. Ergometrine 0.5mg or syntometrine 1 amp IMI provided no hypertension or cardiac disease [repeat once if needed]

Used by medical officer:
4. In women with hypertension or cardiac disease who continue to bleed with atonic uterus despite oxytocin, the risks versus benefits of ergometrine need to be weighed up.
5. Prostaglandin F2α 5mg in 10ml saline, inject 1ml into myometrium, checking carefully that not injecting into a blood vessel
6. Cyclokapron 1g slowly intravenously
7. Misoprostol 400µg sublingually or 600µg per rectum may be considered in the following circumstances:
   1. When no oxytocin or ergometrine is available (eg unplanned home birth)
   2. When all other methods have failed (although there is no evidence of benefit when injectable uterotonics have been given)

INTRODUCTION

Although there are recognised risk factors for postpartum haemorrhage (PPH), PPH may occur unexpectedly in any woman who has given birth. All birth attendants must have the skills and knowledge to manage PPH, and labour wards must have the necessary drugs and equipment readily available.

Because there are several causes for PPH and the cause is often not apparent, management involves a stepwise approach of interventions for all possible causes applied in rapid sequence until the bleeding stops.

This chapter deals with the drugs used to promote contraction of the uterus and to enhance coagulation. The use of drugs must be seen as one element in the holistic management, including:

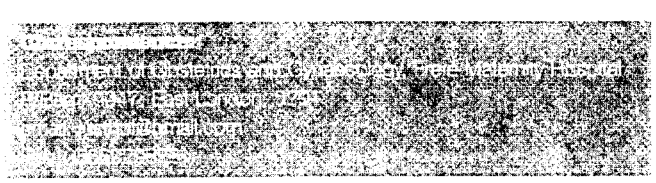
- Active management of 3rd stage including routine oxytocin
- Vigilance for PPH
- Resuscitation and volume replacement
- Surgical measures

The National Department of Health's "Guidelines for maternity Care in South Africa" recommend the following steps:

- Rub up the uterus / bimanual compression
- Infuse oxytocin 20u in 1litre Ringers lactate at 120-240 mL/hour
- Insert a urinary catheter

If the uterus remains soft:

- Ergometrine 0.5mg or syntometrine 1 amp IMI [repeat once if needed]
- Misoprostol 400 to 600µgm per rectum or sublingually
- Prostaglandin F2α 5mg in 10ml saline, inject 1ml into myometrium



"Rubbing up" the uterus (uterine massage) is performed by firmly massaging the uterus through the mother's abdominal wall. It is thought to promote contraction by stimulating release of prostaglandins from decidual lysosomes. When oxytocin is not available, suckling or nipple stimulation may be tried, as it stimulates the release of endogenous oxytocin from the posterior pituitary gland.

Two drugs have been used to enhance coagulation in cases of PPH unresponsive to routine management: Tranexamic acid and recombinant factor VIIa

This chapter will discuss the use of all the above drugs in more detail.

The WHO has published guidelines for the management of PPH based on a review of the evidence by an expert panel in November 2008. This chapter will be based on the WHO recommendations as the evidence reviewed by the panel included several large randomized trials not published to date.

Uterotonic drugs

Most use of uterotonic drugs for the treatment of PPH is based on extrapolation from evidence of effectiveness for the prevention of PPH, in the absence of direct evidence from trials of the treatment of PPH.

For prevention of PPH, syntometrine compared with oxytocin is associated with a trend to reduced blood loss >1000ml (odds ratio (OR) 0.78, 0.58-1.03); no difference in blood transfusion (OR 1.37, 0.89 to 2.10), and less use of additional uterotonics (risk ratio (RR) 0.83, 0.72-0.96), but more side effects, particularly hypertension (RR 2.40, 1.58-3.64).[3]

Oxytocin compared with ergometrine is associated with no statistically significant difference in blood loss >1000ml (RR 1.09, 0.45-2.66) and use of additional uterotonics (RR 1.02, 0.67-1.55); and fewer adverse side effects: vomiting (RR 0.09, 0.05-0.16); elevated blood pressure (RR 0.01, 0.00-0.15). There were insufficient data to compare the outcome blood transfusion.[3,4]

There were no clear benefits for the use of carbetocin[4], intramuscular prostaglandins[5] or sulprostone[3,7], over oxytocin and/or ergometrine.

For prevention of PPH, misoprostol (400 to 800 mcg) compared with injectable uterotonics is associated with increased blood loss of ≥ 1000ml (RR 1.32; 95% CI 1.16-1.51), but no statistical difference in the incidence of severe morbidity, including maternal death (RR 1.00, 95% CI 0.14-7.10)5.[5]

Recommendation

Based on this indirect evidence, for the management of PPH the WHO strongly recommended:

- Oxytocin rather than ergometine or syntometrine as first line
- Ergomentrine or syntometrine as second line
- A prostaglandin as third line

Review of direct evidence of the effectiveness of misoprostol for treatment of PPH (including unpublished trials) found the following:

- For women who had received oxytocin during the third stage of labour, adjunctive use of misoprostol compared with placebo had no significant effect on additional blood loss ≥ 500 mls (RR: 0.83, 95% CI: 0.64-1.07), additional blood loss ≥ 1000 mls (RR: 0.76, 95% CI: 0.43-1.34) and blood transfusion (RR: 0.96, 0.77-1.19).[8,9,10,11]
- For women who had not received oxytocin during the third stage of labour, misoprostol 800 µg sublingually compared with oxytocin 40 IU IV had an increased risk of additional blood loss ≥ 500 mls (RR: 2.84 (95% CI: 1.63-5.01) and receiving additional therapeutic uterotonics (RR: 198, 95% CI: 1.31-2.99); and a trend to more blood transfusion (RR: 1.58, 95% CI: 0.98-2.55). In terms of side effects 66/488 women receiving misoprostol experienced temperature above 40°C compared to 0/490 with oxytocin. Most of the high temperature cases occurred in Ecuador. There were seven cases of delirium in women with high temperature.[12]

Recommendation

Based on this direct evidence, the WHO strongly recommended that oxytocin alone should be used for the treatment of PPH in preference to adjunct misoprostol.

The panel recognized that there may be settings where oxytocin is not available. It encouraged health-care decision-makers in these settings to strive to make oxytocin available. However, because the use of an uterotonic is deemed essential for the treatment of PPH due to atony, it recommended that misoprostol may be used until such time that oxytocin can be made available for this indication. There was lack of consensus as to whether 800 mcg sublingually or a lower dose should be recommended as the maximum safe dose

Prostaglandin F2α

Prostaglandin F2α intramyometrially has been used empirically as a last resort when all else has failed, though there is no direct evidence for its effectiveness. Because of the risk of dangerous adverse effects if given intravenously, a very small dose (1ml of a solution of 5mg in 10ml saline) is injected transabdominally into the myometrium, taking care to draw back to ensure that the needle in not in a blood vessel.

Tranexamic acid

Tranexamic acid is an anti-fibrinolytic agent used in surgery to reduce blood loss and the need for blood transfusion. The WHO panel found that a systematic review of randomized controlled trials showed that in surgical patients tranexamic acid reduced the risk of blood transfusion by 39%.[13] Another Cochrane review showed that tranexamic acid reduced heavy menstrual bleeding without increase in side-effects.[14]

Subsequent to the WHO consultation, a systematic review of tranexamic acid for postpartum bleeding identified three randomised controlled trials involving 461 participants. Tranexamic acid compared with no treatment reduced blood loss by 92 ml (95%CI 76 to 109). However, in all three trials, allocation concealment was either inadequate or unclear.[15]

A recent randomized trial found that tranexamic acid compared with placebo reduced post-caesarean section blood loss by 9.1ml and increased the 24 hour haemoglobin level by 0.8g/dl. No complications or side effects were reported in either group.[16]

Recommendation (weak)

- Tranexamic acid may be offered as a treatment for PPH if uterotonic options have failed, or trauma is thought to be contributing to the bleeding. Further research is needed.

Recombinant Factor VIIa

There is limited evidence regarding the effectiveness of recombinant factor VIIa for treatment of PPH. In two observational studies , women treated with recombinant factor VIIa after receiving conventional treatments had a trend to reduced risk of death (OR 0.38, 95% CI 0.09-1.60).[16]

A high rate of thrombotic events has been reported in patients receiving off-label use of recombinant factor VIIa.[17]

Recommendation

There is not enough evidence to make any recommendation regarding the use of recombinant FVIIa for the treatment of PPH. It is prohibitively expensive.

Summary

The following sequence of drugs may be used as part of the management of postpartum haemorrhage

Used by midwife:

8. If not recently given as prophylaxis and drip not yet up, oxytocin 10u im
9. Iv infusion oxytocin 20u in 1000ml Ringers lactate or saline at 120-240 mL/hour
10. Ergometrine 0.5mg or syntometrine 1 amp IMI provided no hypertension or cardiac disease [repeat once if needed]

Used by medical officer:

11. In women with hypertension or cardiac disease who continue to bleed with atonic uterus despite oxytocin, the risks versus benefits of ergometrine need to be weighed up. An empirical compromise is to give very small doses im and repeat if needed while monitoring the blood pressure. Dilute 0.5mg ergometrine to 10ml or 0.2mg to 4ml and give 1ml (=0.05mg) im at a time
12. Prostaglandin F2 5mg in 10ml saline, inject 1ml into myometrium, checking carefully that not injecting into a blood vessel
13. Cyclokapron 1g slowly intravenously

Misoprostol is much less effective than oxytocin and has dose-related side-effects including hyperpyrexia. Once oxytocin has been used an additional benefit of misoprostol is unlikely.

Misoprostol 400µg sublingually or 600µg per rectum may be considered in the following circumstances:

- When no oxytocin or ergometrine is available (eg unplanned home birth)
- When all other methods have failed

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Prevention of postpartum hemorrhage in the absence of uterotonics

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Although effective methods to prevent postpartum hemorrhage are available, deaths from postpartum hemorrhage remain most common in areas where access to health services is poorest. Global access to uterotonic drugs is unachievable in the foreseeable future, and questions of safety and dosage of other methods remain to be resolved [1]. The need exists to investigate simple measures which can be applied universally at the community level to reduce the global burden of postpartum haemorrhage.

Potential strategies and current evidence

1. *Uterine fundal compression ('Crede manoeuvre').* This method has been condemned as dangerous for decades, but is commonly practiced in some parts of the world [2]. Scientific evidence regarding supposed benefits and risks is lacking; however, a protocol for a Cochrane review of the topic has been published [3].
2. *Controlled cord traction without uterotonic administration.* This method has also been condemned because of concern about uterine inversion, but also is commonly practiced in some parts of the world [2], without evidence for or against its use.
3. *Uterine massage.* Uterine massage after delivery of the placenta was advised in the ICM/FIGO Joint Statement on Management of the Third Stage of Labour to Prevent Postpartum Haemorrhage [4]. Massage is thought to stimulate uterine contraction, possibly through stimulation of local prostaglandin release. However, little empirical research exists that evaluates the effectiveness of this method, either as an adjunct to routine uterotonics, or in the absence of uterotonics.

We performed a small pilot study to determine the effectiveness of sustained uterine massage (every 10 minutes for 60 minutes after birth) as an adjunct to oxytocinin for reducing postpartum haemorrhage [5]. The study, a randomized trial conducted in the labor ward of Assiut University Hospital in Egypt, showed reductions in blood loss and other outcomes similar to those which have been achieved with various uterotonic drugs (Table 1). However, because of the relatively small numbers, the confidence limits were wide. These results need to be confirmed by a trial with sufficient numbers to

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Table 1 Comparison of outcomes following sustained uterine massage or no massage

	Massage group (N=98)	Control group (N=102)	Significance	RR	95% Confidence interval
PPH (>500 ml)	4 (4%)	8 (8%)	NS	0.52	0.16, 1.67
Additional uterotonic	5 (5%)	26 (25%)	$P < 0.001$	0.20	0.08, 0.50
Mean blood loss up to 60 minutes postpartum (ml)	204.29 ± 121.40	281.66 ± 173.06	$P < 0.001$		

estimate the effects of sustained uterine massage with greater precision, both with and in the absence of uterotonics.

If found effective, sustained uterine massage could be promoted as a method of reducing postpartum haemorrhage at community level when uterotonics are not available.

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BRIEF COMMUNICATION

Uterine massage and postpartum blood loss

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KEYWORDS
Uterine massage;
Active management of the third stage of labor;
Postpartum hemorrhage;
Uterine atony;
Randomized clinical trial

Postpartum hemorrhage (PPH) is a major cause of maternal mortality and morbidity worldwide. Uterine massage is thought to stimulate uterine contraction, possibly through stimulation of local prostaglandin release and thus to reduce hemorrhage.

The objective of the randomized trial reported here was to determine the effectiveness of intermittent uterine massage after delivery of the placenta to reduce postpartum blood loss and the need for additional uterotonics. The study was conducted in the labor ward of the Department of Obstetrics and Gynecology, Assiut University Hospital, during June and July 2005.

Pregnant women admitted in labor were approached and given information about the study and were invited to participate. Those who agreed were asked to sign an informed consent. If the labor progressed to spontaneous vaginal delivery without obvious genital tract trauma, women were randomly allocated to one of two groups:

1. Routine active management with oxytocin 10 IU I.V. or I.M. (Syntocinon, NOVARTIS), immediate cord clamping and controlled cord traction;
2. Combined routine active management plus intermittent uterine massage. Massage was done every 10 min for 60 min and took the form of manual stimulation of the whole surface of the uterus using steady repetitive movements, as firmly as can be achieved without causing distress to the mother, till the uterus became contracted.

A plastic drape was placed under the woman's buttocks to collect all blood loss after delivery of the baby for 30 and 60 min. Computer-generated random allocation was by means of serial numbered closed envelopes using a random table. Approval of the Ethics Committee of the Faculty of Medicine, Assiut University was obtained.

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Table 1 Blood loss after delivery

	Study group ($N=98$)	Control group ($N=102$)	Significance (P value)
Mean blood loss during 3rd stage up to 30 min postpartum (ml)	168.78 ± 90.51	210.39 ± 146.18	$P=0.017$
Mean blood loss during 3rd stage up to 60 min postpartum (ml)	204.29 ± 121.40	281.66 ± 173.06	$P<0.001$

Table 2 Incidence of postpartum hemorrhage and need for additional uterotonics

	Study group ($N=98$)	Control group ($N=102$)	Significance	RR	95% Confidence limit
PPH (>500 ml)	4 (5%)	8 (7%)	NS	0.52	0.16, 1.67
Additional uterotonic	5 (6%)	26 (25%)	$P<0.001$	0.20	0.08, 0.50

At baseline, there were no statistically significant differences between the two groups in their mean age, parity, gestational age at delivery, oxytocin use during labor, mode of delivery, birth weight as well as in the mean duration of the third stage of labor.

At 30 and 60 min after delivery the mean blood loss was less in the uterine massage group than in the control group, and the difference was only statistically significant (Table 1).

There were 4 cases of atonic postpartum hemorrhage (>500 ml) at 60 min after delivery in the uterine massage group versus 8 cases in the non-massage group. There was 80% reduction in the use of additional uterotonics in the uterine massage group in comparison to the non-massage group (RR 0.20, 95% CI 0.08, 0.50) (Table 2).

This is thought to be the first randomized clinical trial to assess the effect of uterine massage on blood loss after delivery. The trial showed that persistent uterine massage reduced the amount of blood loss and the use of additional uterotonics.

Limitations of this study include the small sample size and the fact that, because of the nature of the intervention, staff could not be blinded to the group allocation. The chance of bias with respect to blood loss assessment was minimized by using objective, direct measurement. However, the use of other interventions could have been influenced by knowledge of the group allocation. Larger studies are needed to ascertain with more precision the effect of uterine massage on more substantive outcomes, and also the effectiveness in the absence of availability of injectable uterotonics.

The potential for the use of routine uterine massage on a wide scale, particularly where uterotonics are not available, has profound public health implications.

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CLINICAL ARTICLE

Uterine massage to reduce postpartum hemorrhage after vaginal delivery

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ABSTRACT

Objective: To determine the effectiveness of sustained uterine massage started before delivery of the placenta in reducing postpartum hemorrhage. *Methods:* A randomized controlled trial conducted in Egypt and South Africa between September 2006 and February 2009. A total of 1964 pregnant women were randomly allocated to 1 of 3 treatment groups: intramuscular oxytocin, sustained uterine massage, or both treatments. Blood loss within 30 minutes of delivery was recorded. *Results:* The incidence of blood loss of 300 mL or more within 30 minutes of delivery was significantly higher in the massage group than in the massage plus oxytocin (RR 1.88; 95% CI, 1.29–2.74 in Assiut, and RR 1.3; 95% CI, 1.00–1.68 in SA) and the oxytocin only group (RR 1.7; 95% CI, 1.11–2.61 in Assiut, and RR 2.24; 95% CI, 1.54–3.27 in SA). In both centers, use of additional uterotonics was significantly higher in the uterine massage group compared with the other 2 groups. *Conclusion:* Uterine massage was less effective than oxytocin for reducing blood loss after delivery. When oxytocin was used, there was no additional benefit from uterine massage. The effectiveness of uterine massage in the absence of oxytocin was not studied. ACTRN: 12609000372280.
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1. Introduction

Postpartum hemorrhage is a major cause of maternal mortality and morbidity, particularly in under-resourced areas. In Egypt, postpartum hemorrhage is responsible for about 30% of maternal deaths [1]. The South African National Committee for Confidential Enquiries into Maternal Deaths analyzed 4077 reported maternal deaths from 2005 to 2007 and, overall, 9.7% of deaths were due to postpartum hemorrhage [2].

In well-resourced health services, deaths from postpartum hemorrhage are extremely rare because effective preventative methods are available. Deaths from postpartum hemorrhage remain most common in areas where access to health services is poorest. As such, it is vital to investigate simple measures that can be applied universally at community level to reduce the incidence of postpartum hemorrhage.

Guidelines for the prevention of postpartum hemorrhage, such as the joint statement of the International Confederation of Midwives and the International Federation of Gynecology and Obstetrics [3], recommend routine massage of the uterus after delivery of the placenta. Massage is thought to stimulate uterine contraction, possibly through stimulation of local prostaglandin release, and thus reduce hemorrhage. However, there has been very little empirical research to evaluate the effectiveness of this method.

The aim of the present study was to determine the effectiveness of sustained uterine massage, started before delivery of the placenta, in reducing postpartum hemorrhage.

2. Materials and methods

This trial was conducted between September 1, 2006, and February 28, 2009, at the Department of Obstetrics and Gynecology, Women's Health Center, Assiut, Egypt, and the Department of Obstetrics and Gynecology, East London Hospital Complex, East London, South Africa. Ethical approval for the study was obtained from the Ethics Committee, Faculty of Medicine, Assiut University and East London Hospital Complex, South Africa. Pregnant women who were expected to give birth normally were given information about the study and invited to participate. Those who agreed gave written informed consent.

Exclusion criteria were medical complications such as hypertension and diabetes, previous cesarean delivery, and an abdominal wall that was not thin enough to allow easy palpation of the uterus after delivery.

If labor progressed to spontaneous vaginal delivery, the women were allocated to 1 of 3 groups by selecting the next number in a computer-generated random number sequence; the allocated group was noted inside opaque sealed envelopes.

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Group 1 received routine management with 10 IU of oxytocin given intramuscularly according to routine hospital policy (usually after delivery of the anterior shoulder or after delivery of the neonate). Group 2 was given sustained uterine massage shortly after delivery by the research midwives; massage was sustained for 30 minutes and involved manual stimulation of the whole surface of the uterus using steady repetitive movements, as firmly as could be achieved without causing distress to the mother. Injections of oxytocin were delayed until after the 30-minute period of massage and blood collection, unless blood loss of 500 mL was measured before that time. Group 3 received combined routine management with oxytocin plus sustained uterine massage.

In all 3 groups, the umbilical cord was clamped soon after delivery of the neonate, and the placenta was delivered by controlled cord traction when the uterus became contracted. In Assiut, a calibrated plastic drape was placed under the woman's buttocks to collect the blood lost within 30 minutes after delivery of the neonate. At the East London Hospital Complex, a low profile plastic "fracture" bedpan was placed under the mother's buttocks to collect the blood lost within 30 minutes of delivery. Suturing was conducted as required.

The time of delivery of the neonate, group allocation, and delivery of the placenta were noted. Thirty minutes after delivery, the drape or bedpan was removed and the volume of blood was measured in a measuring jar.

The following data were collected age, parity, duration of pregnancy, use of uterotonics for induction of labor, use of uterotonics for augmentation of labor, weight and height of the mother after the birth, weight of the neonate, time of delivery, time of opening of the group allocation envelope, time of commencing massage, time of discontinuing massage, time of oxytocin administration, time of placental delivery, use of episiotomy, volume of blood in the drape or bedpan after 30 minutes, and use of additional uterotonics. Other interventions for hemorrhage such as manual removal of placenta and bimanual uterine compression were also noted.

The primary outcomes were blood loss of 300 mL or more within 30 minutes, and delivery of the placenta 30 or more minutes after the birth. Secondary outcomes were blood loss of 500 mL or more in 30 minutes, blood loss of 1000 mL or more in 30 minutes, use of additional uterotonics or other procedures for management of postpartum hemorrhage, hemoglobin level after 12–24 hours of less than 8 g in 100 mL and less than 10 g in 100 mL (South African site only), blood transfusion, manual removal of placenta or the placenta not delivered after 30 minutes, maternal morbidity, and adverse effects (nausea, vomiting, pain or discomfort).

All women received interventions to promote uterine contraction (oxytocin, sustained uterine massage, or both). Blood loss was closely monitored in all women, and any interventions needed for postpartum hemorrhage were started without delay.

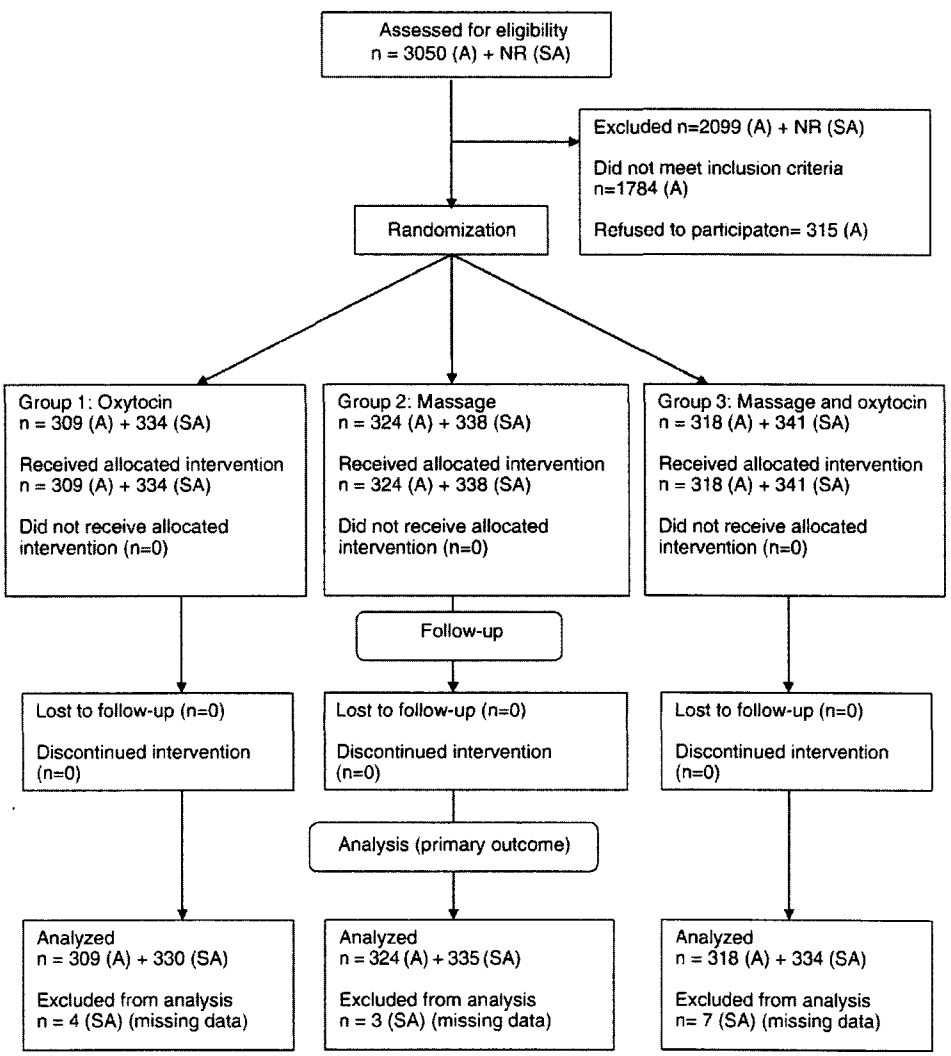

Fig. 1. Flow chart of patients at each stage of the trial from each center: Assiut (A) and South Africa (SA). Abbreviation: NR, not recorded.

The confidentiality of participants was maintained. Participants were free to decline or withdraw from the study at any time without giving reason, with the assurance that the care they received would not be compromised in any way. The sample size calculation was based on our previous studies in which blood loss of greater than 500 mL within 60 minutes occurred in 13.5% of women receiving oxytocin [6]. We expected the proportion of women with 300 mL of blood loss after 30 minutes to be at least as high. A sample size of 650 women per group would be sufficient to show a reduction from 13.5% to 8.5% with oxytocin plus sustained uterine massage. The total sample size required was 1950.

Data were entered into a spreadsheet and analyzed using Epi Info 2002 (CDC, Atlanta, GA, USA). Outcome data were compared using risk ratios (RR) or mean differences (MD) with 95% confidence intervals (CI) (analogous to $P<0.05$). Because of the expected differences in the populations studied and the practices at the 2 sites, it was decided prospectively to combine the results from Assiut and South Africa by meta-analysis (RevMan version 5.0; Cochrane IMS, Copenhagen, Denmark) if no significant heterogeneity was found ($I^2>50\%$ and $P<0.1$).

3. Results

Participant flow through the trial is shown in Fig. 1. Among 3050 women screened in Assiut, 951 women were recruited; although the number assessed for eligibility and the number of women excluded were not recorded in South Africa, 1013 women were recruited. In total, 1964 women were recruited to the study.

The baseline characteristics of the patients in the 3 groups were similar, except for maternal age in the Assiut study where the mean age of the women in the uterine massage group was lower than in the uterine massage plus oxytocin group (24.16 ± 4.95 vs 25.07 ± 5.31; $P=0.04$) (Table 1).

The outcomes of the trial are shown in Table 2. In Assiut, the incidences of blood loss of 300 mL or more within 30 minutes were 12.9%, 20.7%, and 11.0% in the oxytocin, uterine massage, and uterine massage plus oxytocin groups, respectively. The corresponding values in South Africa were 15.8%, 29.6%, and 22.8%, respectively. The incidence of blood loss of 300 mL or more was significantly higher in the massage group than in the massage plus oxytocin group (RR 1.88; 95% CI, 1.29–2.74 in Assiut, and RR 1.3; 95% CI, 1.00–1.68 in SA) and in the oxytocin only group (RR1.7; 95% CI, 1.11–2.61 in Assiut, and RR 2.24; 95% CI, 1.54–3.27 in SA). There was no significant difference in this primary outcome between the group that received massage plus oxytocin and the group that received oxytocin alone in the third stage of labor in the study in Egypt; however, in South Africa, it appears that massage plus oxytocin was associated with more blood loss than with oxytocin alone (22.8% vs 15.8%; RR 1.57; 95% CI, 1.06–2.33) (Table 2).

In Assiut, there was only 1 case (0.3%) where the placenta was not delivered after 30 minutes, which occurred in the uterine massage group. There were 6 cases of manual removal of the placenta (2 women [0.6%] in the massage group and 4 women [1.3%] in the massage plus oxytocin group). In South Africa, there were 4 cases (1.2%) of manual removal of the placenta in the uterine massage group, 9 cases (2.7%) in the uterine massage plus oxytocin group, and 11 cases (3.4%) in the oxytocin only group. There were no significant differences among the 3 groups. A post hoc analysis of the combined outcome of manual removal of the placenta or placenta not delivered after 30 minutes showed no statistically significant differences among the groups.

For the secondary outcome of blood loss of 500 mL or more within 30 minutes the results were similar to the primary blood loss outcome. The result for the uterine massage plus oxytocin group was similar to that of the oxytocin group, whereas uterine massage was less effective than oxytocin alone or massage plus oxytocin. In the study in South Africa, uterine massage plus oxytocin appeared to be less effective than oxytocin alone (9.6% vs 3.3%; RR 3.07; 95% CI, 1.52–6.21).

In Assiut, the duration of the third stage of labor was not significantly different among the 3 groups, with the median time to placental delivery of 3 minutes in the 3 groups (this data was not collected in South Africa). The use of additional uterotonics was significantly higher in the massage group compared with the other 2 groups.

The numbers were too small for statistical analysis for need for other interventions (manual removal of the placenta and bimanual uterine compression).

Pain or discomfort was reported by 175 (54.0%) women in Assiut who received massage. Few other adverse effects of the treatments were reported by the women or observed (nausea or vomiting). There were no cases of maternal morbidity (e.g. admission to intensive care unit or prolonged hospitalization).

4. Discussion

A previous systematic review [4] assessed the effectiveness of uterine massage after birth and before or after delivery of the placenta, or both, to reduce postpartum blood loss and associated morbidity and mortality. The review included 1 randomized controlled trial [5] in which 200 women was randomized to receive uterine massage or no massage after active management of the third stage of labor. The number of women with blood loss of more than 500 mL was small,

Table 1
Baseline characteristics of patients included in the trial in Assiut and South Africa.[a,b]

Characteristics	Oxytocin (group 1)		Uterine massage (group 2)		Uterine massage and oxytocin (group 3)	
	Assiut (n = 309)	S. Africa (n = 334)	Assiut (n = 324)	S. Africa (n = 338)	Assiut (n = 318)	S. Africa (n = 341)
Age, y	24.31 ± 4.52	27.4 ± 5.8 (n = 331)	24.16 ± 4.95	27.1 ± 5.9 (n = 334)	25.07 ± 5.31	27.5 ± 6.0 (n = 339)
Primiparous	104 (33.5)	104/297 (35.0)	111 (34.2)	113/307 (36.8)	110 (34.6)	106/318 (33.3)
Parity 4+	24 (7.7)	14/297 (4.7)	27 (8.3)	8/307 (2.6)	37 (11.6)	12/318 (3.8)
Duration of pregnancy, wk	38.50 ± 1.88	37.7 ± 3.0 (n = 259)	38.38 ± 1.90	37.9 ± 2.3 (n = 265)	38.35 ± 1.83	37.6 ± 3.1 (n = 277)
Maternal height, cm	155.98 ± 6.90	-	156.13 ± 7.31	-	156.92 ± 7.54	-
Maternal weight after birth, kg	64.73 ± 10.26	-	65.20 ± 10.13	-	65.24 ± 9.61	-
Uterotonics for labor induction	35 (11.3)	10/320 (3.1)	44 (13.6)	10/325 (3.1)	41 (12.9)	12/331 (3.6)
Weight of newborn, g	3161.29 ± 423.4	3198 ± 500 (n = 328)	3147.91 ± 411.3	3141 ± 517 (n = 335)	3187.64 ± 388.1	3166 ± 493 (n = 333)
Spontaneous delivery	307	-	323	-	316	-
Operative vaginal delivery	3	-	1	-	2	-
Episiotomy or perineal tear	134 (43)	-	150 (46.3)	-	142 (44.7)	-

[a] Values are expressed as mean ± SD or number (percentage).
[b] In Assiut the data were complete for all baseline data, so the denominator is the same.

Table 2
Outcomes and comparisons of treatment with oxytocin, uterine massage, or both treatments.[a]

Outcomes	Results			Comparisons		
	Oxytocin (group 1)	Uterine massage (group 2)	Uterine massage + oxytocin (group 3)	Uterine massage vs uterine massage + oxytocin (group 2 vs group 3)	Uterine massage vs oxytocin (group 2 vs group 1)	Uterine massage + oxytocin vs oxytocin (group 3 vs group 1)
Primary outcomes						
Blood loss > 300 mL within 30 minutes						
Assiut	40/309 (12.9)	67/324 (20.7)	35/318 (11.0)	1.88 (1.29–2.74)	1.70 (1.11–2.61)	0.83 (0.51–1.35)
S. Africa	52/330 (15.8)	99/335 (29.6)	76/334 (22.8)	1.30 (1.00–1.68)	2.24 (1.54–3.27)	1.57 (1.06–2.33)
Placenta delivered ≥30 minutes after delivery of newborn						
Assiut	0/309 (0)	1/324 (0.3)	0/318 (0)	2.94 (0.12–72.01)	2.86 (0.12–69.9)	NE
S. Africa	11/325 (3.4)	4/334 (1.2)	9/337 (2.7)	0.45 (0.14–1.44)	0.35 (0.11–1.10)	0.79 (0.33–1.88)
Secondary outcomes						
Blood loss ≥500 mL in 30 minutes						
Assiut	11/309 (3.5)	25/324 (7.7)	9/318 (2.8)	2.73 (1.29–5.75)	2.17 (1.09–4.33)	0.79 (0.32–1.93)
S. Africa	11/330 (3.3)	40/335 (11.9)	32/334 (9.6)	1.25 (0.80–1.93)	3.58 (1.87–6.86)	3.07 (1.52–6.21)
Blood loss ≥1000 mL in 30 minutes						
Assiut	0/309	2/324 (0.6)	0/318	NE	NE	NE
S. Africa	1/330 (0.30)	2/335 (0.60)	3/334 (0.90)	NE	NE	NE
Placenta delivered ≥60 minutes after delivery of newborn						
Assiut	0/309	0/324	0/318	NE	NE	NE
S. Africa	4/325 (1.2)	0/334	0/337	NE	NE	NE
Additional uterotonics						
Assiut	17/309 (5.5)	50/324 (15.4)	19/318 (6.0)	2.58 (1.56–4.28)	2.81 (1.65–4.75)	1.09 (0.58–2.05)
S. Africa	3/313 (0.96)	5/317 (1.6)	2/320 (0.63)	2.52 (0.49–12.91)	1.65 (0.40–6.83)	0.65 (0.11–3.88)
Other procedures for postpartum hemorrhage						
Assiut	0/309	5/324 (1.5)	4/318 (1.3)	1.23 (0.33–4.62)	10.49 (0.58–189.0)	8.75 (0.47–161.8)
S. Africa	1/313 (0.32)	1/316 (0.32)	1/320 (0.31)	1.01 (0.06–16.12)	0.99 (0.06–15.77)	0.98 (0.06–15.57)
Hemoglobin <8 g/dL after 12–24 h						
S. Africa	8/191 (4.2)	9/190 (4.7)	5/191 (2.6)	1.81 (0.62–5.30)	1.13 (0.45–2.87)	0.63 (0.21–1.88)
Hemoglobin <10 g/dL after 12–24 h						
S. Africa	43/191 (22.5)	52/190 (27.4)	43/191 (22.5)	1.22 (0.86–1.73)	1.22 (0.86–1.73)	1.00 (0.69–1.45)
Blood transfusion						
Assiut	2/309 (0.65)	4/324 (1.2)	0/318	8.83 (0.48–163.4)	1.91 (0.35–10.34)	0.19 (0.01–4.03)
S. Africa	2/311 (0.64)	3/318 (0.94)	4/319 (1.26)	0.75 (0.17–3.33)	1.47 (0.25–8.72)	1.95 (0.36–10.57)
Manual removal of placenta or placenta not delivered after 30 minutes						
Assiut	0/309	2/324 (0.6)	4/318 (1.3)	0.49 (0.09–2.66)	4.77 (0.23–98.9)	8.75 (0.47–161.8)
S. Africa	11/325 (3.4)	4/334 (1.2)	9/337 (2.7)	0.45 (0.14–1.44)	0.35 (0.11–1.10)	0.79 (0.33–1.88)

Abbreviation: NE, not estimated.
[a] Data are expressed as number (percentage) unless otherwise indicated. Differences are expressed as risk ratio (RR) or mean difference (95% confidence interval).

with wide confidence intervals and no statistically significant difference (risk ratio 0.52, 95% CI, 0.16–1.67). There were no cases of retained placenta in either group. The mean blood loss was less in the uterine massage group at 30 minutes (MD −41.60; 95% CI, −75.16 to −8.04) and 60 minutes after enrolment (MD −77.40; 95% CI −118.71 to −36.09 mL). The need for additional uterotonics was reduced in the uterine massage group (RR 0.20; 95% CI, 0.08–0.50). The review concluded that uterine massage after delivery of the placenta is advised to prevent postpartum hemorrhage. However, because of the limitations of the 1 trial reviewed, trials with sufficient numbers to estimate the effects of sustained uterine massage with greater precision, both with and in the absence of uterotonics, are needed.

After the recommendations of the systematic review, the present trial was conducted to evaluate the effectiveness of uterine massage when applied before delivery of the placenta. The present trial showed that uterine massage alone was associated with more blood loss within 30 minutes after delivery compared with treatment with oxytocin with or without massage. This finding is in agreement with studies that showed that oxytocin is highly effective for reducing blood loss after birth, and more effective, for example, than misoprostol [6]. In the present study, the use of additional uterotonics was significantly higher in the group that received massage alone compared with the other 2 groups in Assiut. Adding massage to oxytocin had no significant influence on blood loss after delivery. These findings suggest that once oxytocin has been given there is little scope for further reduction in blood loss.

The mean duration of the third stage of labor was similar among the 3 groups. Controlled cord traction was used as part of the management of the third stage of labor for all 3 groups; this procedure might have affected the duration of the third stage of labor.

A possible limitation of the study was that uterine massage may have expelled blood clots more effectively from the uterine cavity, which led to a spuriously raised measurement of blood loss relative to the oxytocin alone group in South Africa. Because of the disparity in the results between the 2 centers, a meta-analysis to combine the results of the 2 centers was not done. Another limitation is that the trial did not compare massage versus no massage without the use of oxytocin, which would have been a useful comparison to see whether uterine massage has any effect on blood loss when oxytocin is not available. However, this approach would be difficult to be accepted or approved ethically in a hospital setting.

In conclusion uterine massage is less effective than oxytocin for reducing blood loss after delivery. When oxytocin is used, there is no evidence of additional benefit from uterine massage. However, the effectiveness of uterine massage in the absence of oxytocin was not studied.

Conflict of interest

The authors declare no conflict of interest.

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Uterine massage for preventing postpartum haemorrhage (Review)

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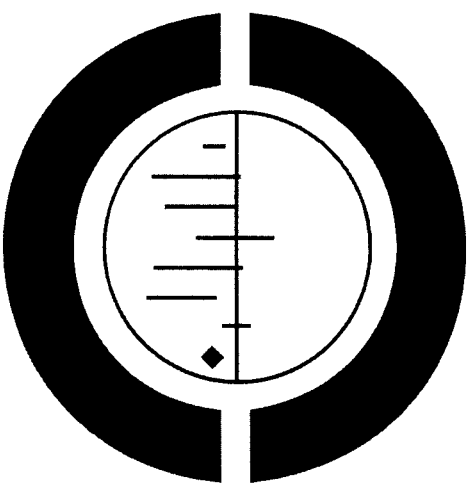

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[Intervention Review]

Uterine massage for preventing postpartum haemorrhage

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ABSTRACT

Background

Postpartum haemorrhage (PPH) (bleeding from the genital tract after childbirth) is a major cause of maternal mortality and disability, particularly in under-resourced areas. In these settings, poor nutrition, malaria and anaemia may aggravate the effects of PPH. In addition to the standard known strategies to prevent and treat PPH, there is a need for simple, non-expensive techniques which can be applied in low-resourced settings to prevent or treat PPH.

Objectives

To determine the effectiveness of uterine massage after birth and before or after delivery of the placenta, or both, to reduce postpartum blood loss and associated morbidity and mortality.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (March 2008), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2007, Issue 2) and PubMed (1966 to June 2007).

Selection criteria

All published, unpublished and ongoing randomised controlled trials comparing uterine massage alone or in addition to uterotonics before or after delivery of the placenta, or both, to non-massage.

Data collection and analysis

Both authors extracted the data independently using the agreed form.

Main results

One randomised controlled trial in which 200 women were randomised to receive uterine massage or no massage after active management of the third stage of labour. The numbers of women with blood loss more than 500 ml was small, with wide confidence intervals and no statistically significant difference (risk ratio (RR) 0.52, 95% confidence interval (CI) 0.16 to 1.67). There were no cases of retained placenta in either group. The mean blood loss was less in the uterine massage group at 30 minutes (mean difference (MD) -41.60, 95% CI -75.16 to -8.04) and 60 minutes after enrolment (MD -77.40, 95% CI -118.71 to -36.09 ml) . The need for additional uterotonics

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was reduced in the uterine massage group (RR 0.20, 95% CI 0.08 to 0.50). Two blood transfusions were administered in the control group.

Authors' conclusions

The present review adds support to the 2004 joint statement of the International Confederation of Midwives and the International Federation of Gynaecologists and Obstetricians on the management of the third stage of labour, that uterine massage after delivery of the placenta is advised to prevent PPH. However, due to the limitations of the one trial reviewed, trials with sufficient numbers to estimate the effects of sustained uterine massage with great precision, both with and in the absence of uterotonics, are needed.

PLAIN LANGUAGE SUMMARY

Uterine massage for preventing postpartum haemorrhage

Bleeding from the genital tract after childbirth (postpartum haemorrhage) is a major cause of maternal mortality and disability in under-resourced areas with poor access to health services. It is the leading cause of maternal mortality in Sub-Saharan Africa and Egypt and yet is largely preventable. In these settings, poor nutrition, malaria and anaemia add to the health risk. Heavy bleeding directly following childbirth or within 24 hours is most common. Possible causes are the uterus failing to contract after delivery (uterine atony), a retained placenta, inverted or ruptured uterus, and cervical, vaginal, or perineal lacerations.

In well-resourced settings haemorrhage is reduced by routine active management of delivery of the placenta, the third stage of labour.

Facilities for resuscitation, blood transfusion and surgical interventions are also available. The 2004 joint statement of the International Confederation of Midwives and the International Federation of Gynaecologists and Obstetricians recommends routine massage of the uterus after delivery of the placenta to promote contraction. This involves placing a hand on the woman's lower abdomen and stimulating the uterus by repetitive massaging or squeezing movements to stimulate uterine contraction.

The present review included one controlled trial that randomly assigned 200 women to either uterine massage or no massage after active management of the third stage of labour, including the routine use of oxytocin.

Uterine massage given every 10 minutes for 60 minutes after birth effectively reduced blood loss, and the need for additional uterotonics, by some 80%. The number of women losing more than 500 ml of blood also appeared to be halved. Two women in the control group and none in the uterine massage group needed blood transfusions.

This one included study had a small sample size so the confidence intervals were wide. The chance of bias with respect to blood loss assessment was minimised by using objective direct measurement.

Disadvantages to massage include the use of staff time and discomfort to the women.

BACKGROUND

Postpartum haemorrhage (PPH) (excessive bleeding from the genital tract after childbirth) is a major cause of maternal mortality and disability, particularly in under-resourced areas (Fawcus 1995). It is the leading cause of maternal mortality in Sub-Saharan Africa (Lazarus 2005). The South African National Committee for the Confidential Enquiries into Maternal Deaths analysed 3406 reported maternal deaths for the years 2002 to 2004. Overall, 9.5% were due to PPH (NCCEMD 2006). In Egypt, in spite of the drop in maternal mortality ratio from 174/100000 live births in 1992 to 1993 to 80/100000 live births in the year 2000 (MOH 2000), PPH is still the leading cause and responsible for 34% of maternal deaths.

Deaths from PPH remain most common in areas where access to health services is poorest. In these settings, poor nutrition, malaria and anaemia may aggravate the effects of PPH. In well-resourced settings with healthier populations and adequate health services, deaths from PPH are extremely rare, as effective methods are available to reduce and treat PPH. These include routine active management of the third stage of labour and facilities for resuscita-

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tion, blood transfusion and surgical interventions. In the 2002 to 2004 South African National Confidential Enquiry into Maternal Deaths, 83% of the 313 deaths from PPH were found to be 'clearly preventable' (NCCEMD 2006). For these reasons, strategies to reduce deaths from PPH have been a focus of attempts to achieve the Millennium Development Goal of reducing maternal mortality by 75% by 2015.

Primary PPH, heavy bleeding directly following childbirth or within 24 hours thereafter, is the most common type of PPH and can be caused by uterine atony, retained placenta, inverted or ruptured uterus, and cervical, vaginal, or perineal lacerations. Uterine atony, when the uterus fails to contract after delivery, is the most important cause of primary PPH (WHO 2000). Methods leading to contraction of the uterus and correction of atony will reduce the amount of bleeding after delivery.

Recommendations for the prevention of PPH such as the joint statement of the International Confederation of Midwives and the International Federation of Gynaecologists and Obstetricians (ICM/FIGO 2004) recommend routine massage of the uterus after delivery of the placenta. Uterine massage involves placing a hand on the woman's lower abdomen and stimulating the uterus by repetitive massaging or squeezing movements. Massage is thought to stimulate uterine contraction, possibly through stimulation of local prostaglandin release and thus to reduce haemorrhage. However, it is not done routinely after delivery in a systematic way. If shown to be effective, it would have important advantages as it is inexpensive and requires no access to medication or other specialised services, and could be used in any location in which women give birth. Disadvantages include the use of staff time, and discomfort caused to women. However, there is very little empirical research to evaluate the effectiveness of this method. There is therefore a need to evaluate systematically the effectiveness of uterine massage for preventing PPH.

OBJECTIVES

To determine the effectiveness of uterine massage after birth and before or after delivery of the placenta, or both, to reduce postpartum blood loss and associated morbidity and mortality.

METHODS

Criteria for considering studies for this review

Types of studies

All published, unpublished and ongoing randomised controlled trials comparing uterine massage alone or in addition to uterotonics before or after delivery of the placenta, or both, to non-massage. Quasi-randomised trials (for example, those randomised by date of birth or hospital number) were to be excluded from the analysis. Studies reported only in abstract form were to be included if sufficient information to evaluate the trial was available. If not, they would be included in the 'Studies awaiting classification' category and be included in analyses when published as full reports.

Types of participants

Women who have given birth vaginally or by caesarean section.

Types of interventions

1. Uterine massage commencing after birth of the baby, or after delivery of the placenta.
2. No intervention or a 'dummy' procedure to mask allocation.

Types of outcome measures

Primary outcomes

1. Blood loss 500 ml or more after enrolment
2. Placenta delivered more than 30 minutes after birth

Secondary outcomes

1. Blood loss 1000 ml or more after enrolment
2. Mean blood loss after enrolment
3. Mean time to placental delivery
4. Use of additional uterotonics or other procedures for management of postpartum haemorrhage
5. Haemoglobin level after 12 to 24 hours less than 8 g/100 ml or blood transfusion
6. Blood transfusion
7. Maternal death or severe morbidity (organ failure, intensive care unit admission for more than 24 hours, major surgery)
8. Women's experience
9. Caregiver's experience
10. Cost

Only outcomes with available data appear in the analysis table. Outcome data that we did not prespecify, but which are reported by the trial authors, were to be labelled as such in the analysis but not used for the conclusions.

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Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (March 2008).

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

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

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

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

In addition, we searched CENTRAL (*The Cochrane Library* 2007, Issue 2), PubMed (1966 to June 2007) using the term 'uterine massage', and searched reference lists of key papers.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

We assessed for inclusion all potential studies identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, consulted an outside person.

Data extraction and management

We designed a form to extract data. The review authors extracted the data using the agreed form. Discrepancies were resolved through discussion. The Review Manager software (RevMan 2008) was used to double enter all the data.

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

Assessment of methodological quality of included studies

We assessed the validity of each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2005). Methods used for generation of the randomisation sequence were described for each trial.

(1) Selection bias (randomisation and allocation concealment)

We assigned a quality score for each trial, using the following criteria:

(A) adequate concealment of allocation: such as telephone randomisation, consecutively-numbered, sealed opaque envelopes;

(B) unclear whether adequate concealment of allocation: such as list or table used, sealed envelopes, or study does not report any concealment approach;

(C) inadequate concealment of allocation: such as open list of random-number tables, use of case record numbers, dates of birth or days of the week.

We decided to exclude trials with inadequate allocation concealment (C).

(2) Attrition bias (loss of participants, for example, withdrawals, dropouts, protocol deviations)

We assessed completeness to follow up using the following criteria:

(A) less than 5% loss of participants;

(B) 5% to 9.9% loss of participants;

(C) 10% to 19.9% loss of participants;

(D) more than 20% loss of participants.

We decided to exclude outcomes with 10% or more missing data.

(3) Performance bias (blinding of participants, researchers and outcome assessment)

We assessed blinding using the following criteria:

1. blinding of participants (yes/no/unclear);
2. blinding of caregiver (yes/no/unclear);
3. blinding of outcome assessment (yes/no/unclear).

Measures of treatment effect

We carried out statistical analysis using the Review Manager software (RevMan 2008). We used fixed-effect meta-analysis for combining data in the absence of significant heterogeneity if trials were sufficiently similar. If heterogeneity was found, this was to be explored by sensitivity analysis followed by random-effects analysis if required.

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Dichotomous data

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

Continuous data

For continuous data, we used the mean difference if outcomes were measured in the same way between trials. We used the standardised mean difference to combine trials that measure the same outcome, but used different methods. If there was evidence of skewness, this was to be reported.

Unit of analysis issues

Cluster-randomised trials

We decided to include cluster-randomised trials in the analyses along with individually randomised trials. However, we did not identify any cluster-randomized trials but if we do in the future, we will use the methods in Appendix 1.

Dealing with missing data

We decided to analyse data on all participants with available data in the group to which they are allocated, regardless of whether or not they received the allocated intervention. If in the original reports participants are not analysed in the group to which they were randomised, and there was sufficient information in the trial report or the information could be obtained from the trial authors, we would attempt to restore them to the correct group.

Assessment of heterogeneity

We decided to apply tests of heterogeneity between trials, if appropriate, using the I^2 statistic. If we had identified high levels of heterogeneity among the trials (exceeding 50%), we would have explored it by prespecified subgroup analysis and performed sensitivity analysis. A random-effects meta-analysis would be used as an overall summary if this was considered appropriate.

Subgroup analyses

We decided to conduct planned subgroup analyses classifying whole trials by interaction tests as described by Deeks 2001.
The plan was to carry out the following subgroup analyses:

1. women delivered vaginally or by caesarean section;
2. comparisons with or without the use of routine oxytocics;
3. uterine massage commenced before or after placental delivery.

Sensitivity analyses

Sensitivity analyses are planned to explore the effect of trial quality assessed by concealment of allocation by excluding studies with inadequate allocation of concealment (rated B) and to assess the possible effect of publication bias by a sensitivity analysis excluding trials not identified from prospective trial registers.

RESULTS

Description of studies

See: Characteristics of included studies.
The review included one small randomised trial conducted in a teaching hospital located in a developing country (Egypt). *See* table of 'Characteristics of included studies'.

Risk of bias in included studies

See table of 'Characteristics of included studies', particularly the 'Methods' section.

The allocation concealment was adequate and there was no loss to follow up. There was no blinding of participants and caregivers. Because outcome assessment was dependent on objective measurement of blood loss and done by the nurses, not the researchers, the risk of bias is low. The methodological quality of this trial is moderate.

Effects of interventions

This review included one trial in which 200 women were randomly allocated to receive uterine massage or no massage after active management of the third stage of labour, including the routine use of oxytocin 10 units. The study was underpowered for precise assessment of the proportion of women with blood loss more than 500 ml, with wide confidence intervals (risk ratio (RR) 0.52, 95% confidence interval (CI) 0.16 to 1.67). There were no cases of retained placenta in either group. The mean blood loss was less in the uterine massage group at 30 (mean difference (MD) -41.60, 95% CI -75.16 to -8.04) and 60 minutes after enrolment (MD -77.40, 95% CI -118.71 to -36.09 ml). The need for additional uterotonics was reduced in the uterine massage group by 80% (RR 0.20, 95% CI 0.08 to 0.50). There were two blood transfusions in the control group and none in the uterine massage group (too few for statistical analysis).

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DISCUSSION

The present review included one small trial which showed that sustained uterine massage (every 10 minutes for 60 minutes after birth) as an adjunct to active management of the third stage of labour is effective in reducing mean blood loss and the need for additional uterotonics. Limitations of the study include the small sample size, thus the confidence intervals were wide. Because of the nature of the intervention, staff could not be blinded to the group allocation. The chance of bias with respect to blood loss assessment was minimised by using objective direct measurement. However, the use of other interventions could have been influenced by knowledge of the group allocation. The study was underpowered to address the primary outcomes of this review, blood loss greater than 500 ml after enrolment and placenta delivered more than 30 minutes after birth.

It would be reasonable to expect that the effectiveness of uterine massage in the absence of uterotonics would, if anything, be more pronounced, but direct evidence was not found.

AUTHORS' CONCLUSIONS

Implications for practice

The joint statement of ICM/FIGO 2004 on management of the third stage of labour, advises uterine massage after delivery of the placenta to prevent postpartum hemorrhage.The data from one small trial reviewed here are consistent with this advice, but the limitations should be recognised.

Implications for research

Due to the limitations of the included trial, trials with sufficient numbers to estimate the effects of sustained uterine massage with greater precision, both with and in the absence of uterotonics, are needed.

ACKNOWLEDGEMENTS

As part of the prepublication editorial process, this protocol has been commented on by three peers (an editor and two referees who are external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Abdel-Aleem 2006

Methods	Randomised clinical trial. Allocation in computer-generated random sequence by numbered, sealed, opaque envelopes. Attrition bias: no. Blinding of participants: no. Blinding of caregiver: no. Blinding of outcome assessment: yes.
Participants	200 women delivered vaginally. Women were enrolled shortly after birth of the baby, by opening the sealed allocation envelope. Setting: labour ward in a University hospital, Assiut, Egypt
Interventions	Uterine massage after delivery of the placenta, every 10 minutes for 60 minutes (98 women). Control group: no intervention (102 women). All women received active management of the third stage of labour including oxytocin 10 units
Outcomes	Blood loss > 500 ml after enrolment. Mean blood loss after enrolment (up to 30 and 60 minutes). Blood loss was measured objectively with a plastic drape placed under the woman's buttocks after birth of the baby Placenta delivered > 30 minutes after birth. Use of additional uterotonics. Blood transfusion.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

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DATA AND ANALYSES

Comparison 1. Uterine massage after placental delivery versus no massage: vaginal birth

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Blood loss 500 ml or more after enrolment	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.16, 1.67]
1.1 Routine uterotonic used	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.16, 1.67]
1.2 No routine uterotonic	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Placenta delivered more than 30 minutes after birth	1	200	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.1 Routine uterotonic used	1	200	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2 No routine uterotonic	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Blood loss 1000 ml or more after enrolment	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Mean blood loss in 30 minutes after enrolment	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Routine uterotonics used	1	200	Mean Difference (IV, Fixed, 95% CI)	-41.60 [-75.16, -8.04]
4.2 No routine uterotonics	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
5 Mean blood loss in 60 minutes after delivery (ml)	1	200	Mean Difference (IV, Fixed, 95% CI)	-77.40 [-118.71, -36.09]
5.1 Routine uterotonics used	1	200	Mean Difference (IV, Fixed, 95% CI)	-77.40 [-118.71, -36.09]
5.2 No routine uterotonics	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
6 Use of additional uterotonics	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.08, 0.50]
6.1 Routine uterotonics used	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.08, 0.50]
6.2 No routine uterotonics	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Haemoglobin level after 12 to 24 hours less than 8 g/100 ml	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8 Blood transfusion	1	200	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8.1 Routine uterotonics used	1	200	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8.2 No routine uterotonics	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9 Maternal death or severe morbidity	1	200	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.1 Routine uterotonics used	1	200	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.2 No routine uterotonics	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

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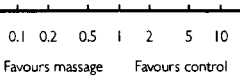
Analysis 1.1. Comparison 1 Uterine massage after placental delivery versus no massage: vaginal birth, Outcome 1 Blood loss 500 ml or more after enrolment.

Review: Uterine massage for preventing postpartum haemorrhage

Comparison: 1 Uterine massage after placental delivery versus no massage: vaginal birth

Outcome: 1 Blood loss 500 ml or more after enrolment

Study or subgroup	Uterine massage n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Routine uterotonic used					
Abdel-Aleem 2006	4/98	8/102		100.0 %	0.52 [0.16, 1.67]
Subtotal (95% CI)	**98**	**102**		**100.0 %**	**0.52 [0.16, 1.67]**
Total events: 4 (Uterine massage), 8 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.10 (P = 0.27)					
2 No routine uterotonic					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Uterine massage), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**98**	**102**		**100.0 %**	**0.52 [0.16, 1.67]**
Total events: 4 (Uterine massage), 8 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.10 (P = 0.27)					



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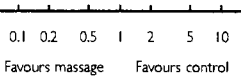
Analysis 1.2. Comparison 1 Uterine massage after placental delivery versus no massage: vaginal birth, Outcome 2 Placenta delivered more than 30 minutes after birth.

Review: Uterine massage for preventing postpartum haemorrhage

Comparison: 1 Uterine massage after placental delivery versus no massage: vaginal birth

Outcome: 2 Placenta delivered more than 30 minutes after birth

Study or subgroup	Uterine massage n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Routine uterotonic used				
Abdel-Aleem 2006	0/98	0/102		0.0 [0.0, 0.0]
Subtotal (95% CI)	**98**	**102**		**0.0 [0.0, 0.0]**
Total events: 0 (Uterine massage), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 No routine uterotonic				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Uterine massage), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**98**	**102**		**0.0 [0.0, 0.0]**
Total events: 0 (Uterine massage), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				



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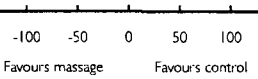
Analysis 1.4. Comparison 1 Uterine massage after placental delivery versus no massage: vaginal birth, Outcome 4 Mean blood loss in 30 minutes after enrolment.

Review: Uterine massage for preventing postpartum haemorrhage

Comparison: 1 Uterine massage after placental delivery versus no massage: vaginal birth

Outcome: 4 Mean blood loss in 30 minutes after enrolment

Study or subgroup	Uterine massage N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Routine uterotonics used							
Abdel-Aleem 2006	98	168.8 (90.5)	102	210.4 (146.2)		100.0 %	-41.60 [-75.16, -8.04]
Subtotal (95% CI)	**98**		**102**			**100.0 %**	**-41.60 [-75.16, -8.04]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.43 (P = 0.015)							
2 No routine uterotonics							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Test for subgroup differences: Not applicable							



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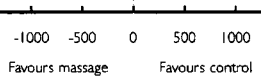
Analysis 1.5. Comparison 1 Uterine massage after placental delivery versus no massage: vaginal birth, Outcome 5 Mean blood loss in 60 minutes after delivery (ml).

Review: Uterine massage for preventing postpartum haemorrhage

Comparison: 1 Uterine massage after placental delivery versus no massage: vaginal birth

Outcome: 5 Mean blood loss in 60 minutes after delivery (ml)

Study or subgroup	Uterine massage N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Routine uterotonics used							
Abdel-Aleem 2006	98	204.3 (121.4)	102	281.7 (173.1)		100.0 %	-77.40 [-118.71, -36.09]
Subtotal (95% CI)	**98**		**102**			**100.0 %**	**-77.40 [-118.71, -36.09]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.67 (P = 0.00024)							
2 No routine uterotonics							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**98**		**102**			**100.0 %**	**-77.40 [-118.71, -36.09]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.67 (P = 0.00024)							
Test for subgroup differences: Not applicable							



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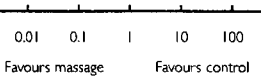
Analysis 1.6. Comparison 1 Uterine massage after placental delivery versus no massage: vaginal birth, Outcome 6 Use of additional uterotonics.

Review: Uterine massage for preventing postpartum haemorrhage

Comparison: 1 Uterine massage after placental delivery versus no massage: vaginal birth

Outcome: 6 Use of additional uterotonics

Study or subgroup	Uterine massage n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Routine uterotonics used					
Abdel-Aleem 2006	5/98	26/102		100.0 %	0.20 [0.08, 0.50]
Subtotal (95% CI)	**98**	**102**		**100.0 %**	**0.20 [0.08, 0.50]**
Total events: 5 (Uterine massage), 26 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.44 (P = 0.00058)					
2 No routine uterotonics					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Uterine massage), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**98**	**102**		**100.0 %**	**0.20 [0.08, 0.50]**
Total events: 5 (Uterine massage), 26 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.44 (P = 0.00058)					



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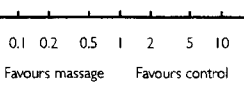
Analysis 1.8. Comparison 1 Uterine massage after placental delivery versus no massage: vaginal birth, Outcome 8 Blood transfusion.

Review: Uterine massage for preventing postpartum haemorrhage

Comparison: 1 Uterine massage after placental delivery versus no massage: vaginal birth

Outcome: 8 Blood transfusion

Study or subgroup	Utrerine massage n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Routine uterotonics used				
Abdel-Aleem 2006	0/98	0/102		0.0 [0.0, 0.0]
Subtotal (95% CI)	**98**	**102**		**0.0 [0.0, 0.0]**
Total events: 0 (Utrerine massage), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 No routine uterotonics				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Utrerine massage), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**98**	**102**		**0.0 [0.0, 0.0]**
Total events: 0 (Utrerine massage), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				



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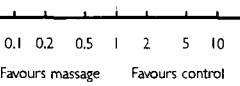
Analysis 1.9. Comparison 1 Uterine massage after placental delivery versus no massage: vaginal birth, Outcome 9 Maternal death or severe morbidity.

Review: Uterine massage for preventing postpartum haemorrhage

Comparison: 1 Uterine massage after placental delivery versus no massage: vaginal birth

Outcome: 9 Maternal death or severe morbidity

Study or subgroup	Uterine massage n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Routine uterotonics used				
Abdel-Aleem 2006	0/98	0/102		0.0 [0.0, 0.0]
Subtotal (95% CI)	**98**	**102**		**0.0 [0.0, 0.0]**
Total events: 0 (Uterine massage), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 No routine uterotonics				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Uterine massage), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**98**	**102**		**0.0 [0.0, 0.0]**
Total events: 0 (Uterine massage), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				



APPENDICES

Appendix 1. Methods to be used for cluster-randomised controlled trials

Their sample sizes will be adjusted using the methods described in Gates 2005 using an estimate of the intracluster correlation coefficient (ICC) derived from the trial (if possible), or from another source. If ICCs from other sources are used, this will be reported and sensitivity analyses conducted to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

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WHAT'S NEW

Last assessed as up-to-date: 30 March 2008.

Date	Event	Description
2 July 2010	Amended	Contact details edited.

HISTORY

Protocol first published: Issue 2, 2007

Review first published: Issue 3, 2008

Date	Event	Description
18 March 2008	Amended	Converted to new review format

CONTRIBUTIONS OF AUTHORS

H Abdel-Aleem (HA) wrote the first draft of the protocol. GJ Hofmeyr (GJH) revised the protocol. HA and GJH independently extracted data. HA wrote the first draft of the final review. GJH revised the final review. M Abdel-Aleem developed the data extraction form, assisted with data extraction and approved the final version.

DECLARATIONS OF INTEREST

H Abdel-Aleem and GJ Hofmeyr are co-authors of a study evaluating the effect of uterine massage on postpartum blood loss (Abdel-Aleem 2006). One of the Pregnancy and Childbirth Group editors (AM Gulmezoglu) evaluated the study for inclusion in the review.

SOURCES OF SUPPORT

Internal sources

- (GJH) Effective Care Research Unit, University of the Witwatersrand, University of Fort Hare, Eastern Cape Department of Health, South Africa.
- Department of Obstetrics and Gynecology, Assiut University Hospital, Assiut, Egypt.

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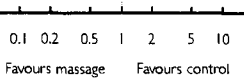
Analysis 1.9. Comparison 1 Uterine massage after placental delivery versus no massage: vaginal birth, Outcome 9 Maternal death or severe morbidity.

Review: Uterine massage for preventing postpartum haemorrhage

Comparison: 1 Uterine massage after placental delivery versus no massage: vaginal birth

Outcome: 9 Maternal death or severe morbidity

Study or subgroup	Uterine massage n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Routine uterotonics used				
Abdel-Aleem 2006	0/98	0/102		0.0 [0.0, 0.0]
Subtotal (95% CI)	**98**	**102**		**0.0 [0.0, 0.0]**
Total events: 0 (Uterine massage), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 No routine uterotonics				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Uterine massage), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**98**	**102**		**0.0 [0.0, 0.0]**
Total events: 0 (Uterine massage), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				



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Their sample sizes will be adjusted using the methods described in Gates 2005 using an estimate of the intracluster correlation coefficient (ICC) derived from the trial (if possible), or from another source. If ICCs from other sources are used, this will be reported and sensitivity analyses conducted to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

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SOURCES OF SUPPORT

Internal sources

- (GJH) Effective Care Research Unit, University of the Witwatersrand, University of Fort Hare, Eastern Cape Department of Health, South Africa.
- Department of Obstetrics and Gynecology, Assiut University Hospital, Assiut, Egypt.

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External sources

- (GJH) HRP-UNDP/UNFPA/WHO/World Bank Special Programme in Human Reproduction, Geneva, Switzerland.

INDEX TERMS

Medical Subject Headings (MeSH)

*Uterus; Labor Stage, Third; Massage [*methods]; Postpartum Hemorrhage [*prevention & control]; Uterine Contraction

MeSH check words

Female; Humans; Pregnancy

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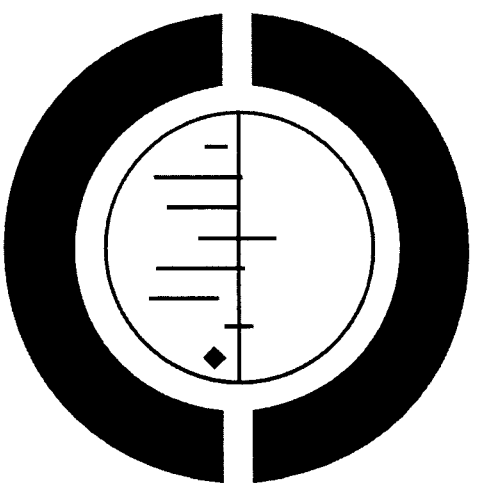
39.

Tranexamic acid for preventing postpartum haemorrhage (Review)

Novikova N, Hofmeyr GJ



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[Intervention Review]

Tranexamic acid for preventing postpartum haemorrhage

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ABSTRACT

Background

Postpartum haemorrhage (PPH) is a common and occasionally life-threatening complication of labour. Several options for preventing PPH are available, but further advances in this field are important, especially the identification of safe, easy to use and cost-effective regimes. Tranexamic acid, which is an antifibrinolytic that is used widely to prevent and treat haemorrhage, merits evaluation to assess whether it meets these criteria. Evidence of effectiveness in preventing PPH might also be extrapolated to use for treatment of PPH (as have other preventive measures).

Objectives

To determine, from the best available evidence, whether tranexamic acid is effective for preventing PPH.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (15 February 2011).

Selection criteria

All published, unpublished and ongoing randomised controlled trials (RCTs) evaluating the use of tranexamic acid alone or in addition to uterotonics in the third stage of labour or during caesarean section to prevent PPH.

Data collection and analysis

Two review authors independently assessed for inclusion all the potential studies identified as a result of the search strategy. We entered the data into Review Manager software and checked for accuracy.

Main results

We included two RCTs. One RCT of unclear quality (involving 273 women) compared tranexamic acid in two doses (0.5 g intravenously and 1 g intravenously) with aminomethylbenzoic acid (0.5 g intravenously) and with no treatment in women who had vaginal birth. We excluded the aminomethylbenzoic acid arm of this trial (92 women). A second RCT of 180 women who underwent caesarean section compared tranexamic acid (1 g intravenously given 10 minutes before incision) with placebo.

Blood loss greater than 400 ml was less common in women who received tranexamic acid after vaginal birth or caesarean section in the dosage of 1 g or 0.5 g intravenously (risk ratio (RR) 0.51; 95% confidence interval (CI) 0.36 to 0.72; two studies, 453 women). Mean

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blood loss was lower in the group of women who received intravenous tranexamic acid postpartum (mean difference (MD) -75.17 ml; 95% CI -108.23 ml to -42.12 ml; two studies, 361 women).

No serious side effects were reported in women who received tranexamic acid in the three included studies.

Authors' conclusions

Tranexamic acid decreases postpartum blood loss after vaginal birth and after caesarean section based on two RCTs of unclear quality which reported on only a few outcomes. Further investigations are needed to confirm efficacy and safety of this regimen for preventing PPH. These results also provide a basis for the investigation of tranexamic acid for the treatment of PPH.

PLAIN LANGUAGE SUMMARY

Tranexamic acid for preventing bleeding after delivery

Tranexamic acid is used to decrease blood loss in surgery and health conditions associated with increased bleeding. This review found that tranexamic acid is also effective in reducing blood loss after a mother gives birth. One study of 400 women (273 women were included in the analysis for purpose of this review), compared use of tranexamic acid in two different doses (1 g and 0.5 g given intravenously) to no such treatment. Tranexamic acid was given two to three minutes after the vaginal delivery of the baby, which is when the mother is most at a risk of excessive bleeding related to the childbirth. In another study (involving 180 women), the use of tranexamic acid was compared with no treatment in women who were undergoing caesarean section. Tranexamic acid was given 10 minutes before incision. The mean blood loss was lower in women who received tranexamic acid compared to women who did not. The higher dose of tranexamic acid tended to cause mild side effects such as nausea and vomiting for a very few of the women. Women who received a lower dose of tranexamic acid had no side effects. More research is needed.

BACKGROUND

Description of the condition

Postpartum haemorrhage (PPH) remains a leading cause of maternal mortality, especially in developing countries (Ronsmans 2006). In confidential enquiries into maternal deaths in South Africa (2005 to 2007) (Confidential enquiries 2006), 383 maternal deaths due to PPH were reported and the majority of these were considered to be preventable. Of these deaths, 67 (17.5%) were caused by uterine atony, where uterotonics were required to control the bleeding. Other cases of maternal death from PPH were due to uterine rupture (37 in women with previous caesarean sections and 43 in women without previous caesarean sections), retained placenta (88), inverted uterus (seven), and other genital tract trauma including caesarean section (141). The great majority were thus not due to uterine atony, and attempts to address the problem need to go beyond the use of uterotonic drugs. Because of the difficulty of randomised trials in women presenting with PPH, the use of tranexamic acid for preventing PPH in high-risk women could be regarded as a proxy for assessing its use for treating PPH. In particular, high-risk factors which may not be responsive to uterotonics, such as placenta praevia and lacerations from instrumental delivery, may respond to tranexamic acid. If tranexamic acid is found to be effective in the prevention of PPH in such high-risk women, its use could be extrapolated to the treatment of PPH (as has been the case for most treatments for PPH, such as oxytocin and ergometrine).

Description of the intervention

Tranexamic acid could be used in addition to current prophylactic uterotonic drugs in the third stage of labour, given intravenously to reduce the blood loss. It is used in the dose of 10 mg/kg given intravenously immediately after delivery of the baby (Astedt 1987) or in a woman undergoing caesarean section, prior to the skin incision. Tranexamic acid acts within two to three hours after oral administration and immediately after intravenous administration, and its half-life is two to 10 hours (Jurema 2008). The oral route of administration is possible, but it is not ideal in the third stage of labour, when an immediate effect of the drug is required. The sublingual route may be an alternative, but has not to our knowledge been investigated.

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How the intervention might work

Tranexamic acid potentates the blood clotting system and is used to treat and prevent bleeding. The mechanism of action of tranexamic acid is related to its antifibrinolytic effect, which makes this drug potentially very effective in the third stage of labour. During placental delivery, rapid degradation of fibrinogen and fibrin occurs, as well as an increase in the activation of plasminogen activators and fibrin degradation products due to activation of the fibrinolytic system. This activation can last up to six to 10 hours postpartum, which may cause more haemorrhage. The antifibrinolytic effect of tranexamic acid in the third stage of labour could make it a safe and effective alternative or adjunct to other regimens currently used in the third stage of labour for prevention of PPH.

Tranexamic acid could reduce blood loss associated with complications such as placenta praevia and lower genital tract trauma, as well as bleeding from the upper segment placental site. Use of tranexamic acid could potentially have prevented some PPH cases if it was given to women with the risk factors for PPH, as reported in the Cochrane review on treatment of PPH (Mousa 2007). Therefore, it may be particularly useful in preventing cases of PPH due to factors other than uterine atony, where uterotonics will not be effective.

Tranexamic acid is an effective agent for the reduction of blood loss, which has been widely used in various areas of medicine. It is an inhibitor of fibrinolysis that blocks the lysine-binding site of plasminogen to fibrin (Astedt 1987; Longstaff 1994). It has been used to decrease blood loss for many years in cases of haemorrhage, and is reported to reduce intraoperative and postoperative blood loss (Boylan 1996; Karski 1995; Katsaros 1996; Reid 1997; Vacharaksa 2002).

Tranexamic acid is associated with a significant reduction in objective measurements of heavy menstrual bleeding when compared to placebo or other medical therapies (NSAIDS, oral luteal phase progestagens and ethamsylate) according to a Cochrane review (Lethaby 2000).

The side effects described with the use of tranexamic acid include gastrointestinal symptoms such as diarrhoea, nausea and vomiting that occur in about 10% of patients. Rare complications include hypotension, thrombosis, blurred vision, renal cortical necrosis and retinal artery obstruction (Astedt 1987). However, another study reported no side effects associated with tranexamic acid (Bekassy 1990). A Cochrane review on the use of antifibrinolytics for heavy menstrual bleeding reported no rise in side effects with tranexamic acid in comparison to placebo, NSAIDS, oral luteal phase progestagens or ethamsylate (Lethaby 2000). There are concerns about the risk of thromboembolic events associated with the use of tranexamic acid; however, there are no data available from randomised controlled trials (RCTs) which record the frequency of thromboembolic events (Lethaby 2000).

Why it is important to do this review

PPH remains an important cause of maternal morbidity and mortality. It is important to establish safe, inexpensive and easily available methods of PPH prevention. Administration of tranexamic acid intravenously in the third stage of labour may be one of these methods. A particular advantage of tranexamic acid is that its effect is not limited to upper segment placental site bleeding, thus its use does not rely on accurate diagnosis of the site of the bleeding. Current evidence on management of the third stage of labour according to a Cochrane review favours active management involving administration of a prophylactic oxytocic before delivery of the placenta, and usually cord clamping and cutting, and controlled traction of the umbilical cord, over passive management: allowing the placenta to deliver spontaneously or aiding by gravity or nipple stimulation (Prendiville 2000). Oxytocin is beneficial for the prevention of PPH. There are insufficient data in favour of ergot alkaloids alone compared to either oxytocin alone, or to ergometrine-oxytocin according to another Cochrane review of management of the third stage of labour (Cotter 2001).

Tranexamic acid is a cost-effective drug. A study on total hip arthroplasty reported saving blood transfusion and money (47 Euro per patient) in cases where tranexamic acid was used prophylactically prior to surgery (Johansson 2005). Using tranexamic acid before caesarean section may reduce the blood loss as well.

Use of tranexamic acid for preventing PPH may contribute to reduction in blood product use, which is associated with multiple risks (transfusion reactions, transmission of blood-borne viruses), is expensive and may be not available when it is needed. In South Africa, most of the maternal deaths due to PPH occur in level one hospitals which do not all have emergency access to formal blood transfusion services. Cost savings could also be gained from avoiding the use of expensive haematological agents such as Factor VIIa, which is establishing its place in the treatment of massive PPH in modern obstetrics despite the extreme cost (Welsh 2008).

OBJECTIVES

To determine, from the best available evidence, whether tranexamic acid is effective for preventing postpartum haemorrhage.

METHODS

Criteria for considering studies for this review

Types of studies

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We included all published, unpublished and ongoing RCTs comparing the use of tranexamic acid alone or in addition to uterotonics in the third stage of labour or prior or during caesarean section to prevent postpartum haemorrhage. We excluded quasi-RCTs (for example, those randomised by date of birth or hospital number) from the analysis.

Types of participants

Women after vaginal or caesarean section birth.

Types of interventions

Trenaxamic acid used for the third stage of labour or at caesarean section to decrease blood loss compared with placebo or other agents such as uterotonics; comparisons of tranexamic acid dosages or routes of administration.

Comparisons

1. Tranexamic acid versus placebo/no treatment
2. Tranexamic acid versus uterotonics
3. Different dosages of tranexamic acid
4. Different routes of administration of tranexamic acid

Types of outcome measures

Primary outcomes

1. Blood loss 500 ml or more
2. Blood loss 1000 ml or more

Secondary outcomes

3. Mean blood loss (ml) (during Caesarean section mean blood loss from placental delivery till two hours postpartum
4. Use of additional medical interventions to control postpartum haemorrhage (PPH)
5. Use of additional surgical interventions to control PPH
6. Maternal haemoglobin concentration (Hb) less than 6 grams/decilitre 24 hours to 48 hours postpartum
7. Maternal death or severe maternal morbidity such as seizure, thromboembolic events, need for intensive care unit admission, hysterectomy, organ failure
8. Mild side effects such as nausea, vomiting, headache, skin reactions
9. Thromboembolic events

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (15 February 2011).

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

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

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

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

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion.

Data extraction and management

We designed a form to extract data. For eligible studies, both review authors extracted the data using the agreed form. We resolved discrepancies through discussion. We entered the data into Review Manager software (RevMan 2011) and checked it for accuracy.

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

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Assessment of risk of bias in included studies

Both review authors independently assessed the validity of each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion.

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

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

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

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

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

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

(3) Blinding of participants, personnel and outcome assessors (checking for possible performance bias)

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

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

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

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

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

(5) Selective reporting (checking for reporting bias)

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

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

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

We describe for each included study any important concerns we have about other possible sources of bias.
We assessed whether each study was free of other problems that could put it at risk of bias:

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

(7) Overall risk of bias

We made explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it likely to impact on the findings. We explored the

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impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Measures of treatment effect

Dichotomous data

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

Continuous data

For continuous data, we used the mean difference (MD) as the outcomes were measured in the same way in both trials.
In future updates of this review, when more studies become available, we will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

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

Crossover trials

Crossover trials are irrelevant for this intervention, and, therefore we have not included them.

Multi-armed trials

When analysing multi-armed trials, we have combined all relevant experimental intervention groups of the study into a single group and all relevant control intervention groups into a single control group. If the authors considered one of the arms irrelevant, we excluded it from analysis.

Dealing with missing data

For included studies, we have noted levels of attrition. We planned to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.
For all outcomes, we have carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we have attempted to include all participants randomised to each group in the analyses, and to analyse all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We planned to use the I^2 statistic to measure heterogeneity among the trials in each analysis (with greater than 50% indicative of substantial heterogeneity). In future updates of this review, as more data become available we will assess statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if I^2 is greater than 30% and either T^2 is greater than zero, or there is a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

In future updates of this review, if there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually, and use formal tests for funnel plot asymmetry. For continuous outcomes we will use the test proposed by Egger 1997, and for dichotomous outcomes we will use the test proposed by Harbord 2006. If we detect asymmetry in any of these tests or by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2011). We used fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect, i.e. where trials are examining the same intervention, and we judged the trials' populations and methods sufficiently similar. In future updates of this review, if there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if we detect substantial statistical heterogeneity, we will use random-effects meta-analysis to produce an overall summary if we consider an

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average treatment effect across trials clinically meaningful. We will treat the random-effects summary as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful we will not combine trials.

If we use random-effects analyses in future updates of this review, we will present the results as the average treatment effect with its 95% CI, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

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

We plan to carry out the following subgroup analyses:

We will compare the outcomes such as mean blood loss greater than 1000 ml and thromboembolic events in subgroups of women delivered vaginally and by caesarean section. We will also compare the above-mentioned outcomes between subgroups with and without routine oxytocics.

For fixed-effect inverse variance meta-analyses we will assess differences between subgroups by interaction tests. For random-effects and fixed-effect meta-analyses using methods other than inverse variance, we will assess differences between subgroups by inspection of the subgroups' confidence intervals; non-overlapping confidence intervals indicate a statistically significant difference in treatment effect between the subgroups.

Sensitivity analysis

In future updates we will perform sensitivity analyses for aspects of the review that might affect the results, for example where there is a risk of bias associated with the quality of some of the included trials; or to explore the effects of fixed-effect or random-effects analyses for outcomes with statistical heterogeneity; and to explore the effects of any assumptions made, such as the value of the ICC used for cluster-randomised trials.

We will perform sensitivity analysis for the primary outcomes (mean blood loss greater than 500 ml and greater than 1000 ml).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

An updated search in February 2011 found three new reports. We have excluded all three studies (Gobbur 2011; Gohel 2007; Sekhavat 2009). This updated review now comprises two included studies and three excluded studies. For further details see Characteristics of included studies and Characteristics of excluded studies.

Included studies

We found one RCT (Yang 2001) investigating the efficacy of tranexamic acid for preventing postpartum haemorrhage in women who had vaginal birth. This study included 400 women with term singleton pregnancy, vertex presentation, spontaneous delivery who received 10 units of oxytocin immediately following delivery of their babies' shoulders. The women were allocated to four groups: group one received tranexamic acid 1 g intravenously; group two received 0.5 g tranexamic acid intravenously; group three received aminomethylbenzoic acid 0.5 g intravenously; and group four did not receive any treatment. The randomisation was not described in the study, which was not blinded. For more information *see* Characteristics of included studies. As the results of group three were not included in this review, the effective sample size for this review was 273 women.

We identified an RCT (Gai 2004) investigating the efficacy of tranexamic acid in reducing blood loss during caesarean section. This study included 180 primigravid women with term singleton pregnancy without severe medical or surgical complication, history of thromboembolic disorders, abnormal placenta, pregnancy complications (pre-eclampsia, macrosomia, polyhydramnios), or myoma. Women in the intervention group received 1 g of tranexamic acid by slow intravenous infusion 10 minutes prior to caesarean section incision. The randomisation was done using a randomised consecutive numbered chart. The study was not blinded. Women in this trial received routine uterotonics (10 units of oxytocin intravenously and 20 units of oxytocin into the uterine wall) after delivery of the baby.

Excluded studies

We excluded three trials (Gobbur 2011; Gohel 2007; Sekhavat 2009).

The first trial (Gohel 2007) on the use of tranexamic acid prior to Caesarean Section incision was quasi-randomised (the rule of odds and even was used for randomisation).

The second trial by Gobbur and co-authors (Gobbur 2011) was only published in abstract form. Neither randomisation, nor allocation concealment were described.

The third trial by Sekhavat and co-authors (Sekhavat 2009) was quasi-randomised (randomisation was done by the rule of odds and even) and did not supply any information on allocation concealment. The outcomes reported were not consistent with our

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review. The blood loss reported in this trial was reported only after cesarean section. The authors have reported the mean haemoglobin concentration after cesarean section, though in this review we decided to report the number of cases with haemoglobin concentration less than six milligrams per decilitre 24 hours after cesarean section.

Risk of bias in included studies

The studies were not blinded. Allocation concealment was not described. Thus, there is a considerable risk of bias in both included studies.

Effects of interventions

We have included one study (Yang 2001) of 273 women comparing tranexamic acid in two doses (0.5 g intravenously and 1 g intravenously) with no treatment given to women having vaginal birth; one study (Gai 2004) of 180 women comparing tranexamic acid (1 g intravenously) given 10 minutes prior to caesarean section.

Primary outcomes

As blood loss greater than 500 ml was not reported in included studies, we have taken the other authors' outcome of blood loss greater than 400 ml (Gai 2004; Yang 2001) as a proxy for the primary outcome.

Blood loss greater than 400 ml was less common in women who received tranexamic acid after vaginal birth or caesarean section in the dosage of 1 g or 0.5 g intravenously (risk ratio (RR) 0.51; 95% confidence interval (CI) 0.36 to 0.72; two studies, 453 women). See Analysis 1.1.

Women who received tranexamic acid two to three minutes postpartum after vaginal birth in the dosage of 1 g or 0.5 g intravenously had less incidence of blood loss greater than 400 ml (RR 0.38; 95% CI 0.22 to 0.68; one study, 273 women). A similar effect was also observed in women who were undergoing caesarean section. Fewer women had blood loss greater than 400 ml after receiving 1 g of tranexamic acid 10 minutes before caesarean section in comparison to women who did not receive tranexamic acid (RR 0.61; 95% CI 0.39 to 0.96; one study, 180 women).

Secondary outcomes

Mean blood loss was lower in the group of women who received intravenous tranexamic acid postpartum (mean difference (MD) -75.17 ml; 95% CI -108.23 to -42.12; two studies, 361 women). This effect was observed after vaginal birth (MD 71.50; 95% CI -115.17 ml to -27.83 ml; one study, 181 women) and after caesarean section (MD - 80.10; 95% CI -130.68 ml to - 29.52 ml; one study 180 women). See analysis Analysis 1.2.

Mild side effects such as nausea and vomiting were reported in women who received 1 g of tranexamic acid intravenously, but no such effects were reported for women who did not receive any treatment (RR 4.63; 95% CI 0.23 to 95.14; one study, 181 women; not statistically significant) Analysis 1.3.

When comparing different dosages (0.5 g versus 1 g) of intravenous tranexamic acid, there were no statistically significant differences in blood loss greater than 400 ml (RR 2.04; 95% CI 0.80 to 5.21; one study) Analysis 2.1, or mean blood loss (MD -0.40 ml; 95% CI -41.06 ml to 40.26 ml) Analysis 2.2.

No other outcomes defined in our protocol were reported in included studies.

DISCUSSION

Tranexamic acid is used widely to prevent haemorrhage. However, we found only five studies investigating the efficacy of tranexamic acid for preventing of postpartum haemorrhage (PPH).

Our review has found a reduction in postpartum blood loss with the use of tranexamic acid after spontaneous delivery (Yang 2001). This included study is limited to 273 women and looked at the use of tranexamic acid in women having vaginal birth. One arm of this study (92 women) was not included in the analysis as we considered it irrelevant. This group of women was given aminomethylbenzoic acid, which was considered a placebo by the trial authors, though there was also a group that has not received any intervention. We have included the latter group. The study was unblinded, with unclear allocation concealment and sequence generation. Another limitation of this study is exclusion of five cases of macrosomia (fetal weight greater than 4000 g) after randomisation, which could have introduced bias. This study was limited to singleton pregnancies and spontaneous delivery, and it reported on very few of the outcomes.

Another study investigated the use of tranexamic acid in women having caesarean section. It was an unblinded study limited to 180 women (Gai 2004). Women received routine uterotonics, which included 10 units of oxytocin intravenously and 20 units of oxytocin into the uterine wall in this trial.

Only blood loss greater than 400 ml, which differed to the primary outcome selected for this review (greater then 500 ml), as well as mild side effects were reported in Gai 2004 and Yang 2001 trials. The reasons behind a choice of an outcome such as blood loss greater than 400 ml are not clear from these papers. The possibility exists that this end-point may have been chosen retrospectively. Both trials reported on mean blood loss.

All women in all studies received routine uterotonics. No comparison between tranexamic acid and uterotonics was provided, nor was the effect of tranexamic acid in the absence of uterotonics, which may potentially be greater, assessed.

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We were unable to address concerns regarding thromboembolic episodes with the use of tranexamic acid in the postpartum period, as no data are available on this major outcome.

To identify the efficacy and safety, as well as rare and more severe side effects that may be associated with the use of this regimen, a larger study is necessary.

Summary of main results

Subject to methodological shortcomings, tranexamic acid given in the dose of 0.5 to 1 g intravenously was effective in reducing postpartum haemorrhage after vaginal birth and caesarean section with minimal side effects.

AUTHORS' CONCLUSIONS

Implications for practice

The limited evidence presented in this review suggests that tranexamic acid may be an effective drug for reducing postpartum haemorrhage (PPH). Confirmation of these findings would be preferable before tranexamic acid could be recommended for prophylactic use in women at high risk of PPH, or women for whom blood loss needs to be minimised, such as women with anaemia or those who are haemodynamically unstable.

Treatment of PPH is beyond the scope of this review, but in the absence of treatment trials, the results of this review, together with the extensive evidence of safety and effectiveness from the surgical disciplines, may contribute to clinical decisions to use tranexamic acid for the treatment of PPH unresponsive to conventional treatment, particularly when haemorrhage is suspected to be due to genital tract trauma.

Implications for research

Because of the risk of bias in two studies reviewed, an adequately sized, placebo-controlled trail is needed to confirm the positive findings of this review. Further research is needed to examine rare side effects that may be associated with the use of tranexamic acid. Studies assessing tranexamic acid for preventing PPH are also important to allow extrapolation to the role of tranexamic acid in the management of PPH (as has happened with the use of uterotonics such as oxytocin and ergometrine for the treatment of PPH).

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CHARACTERISTICS OF STUDIES

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

Gai 2004

Methods	Randomised controlled trial. Multi-centre (2 centres).
Participants	180 primiparas healthy women at term with singleton who underwent caesarean section.
Interventions	1 g (10 ml) of tranexamic acid diluted in 20 ml 5% glucose given intravenously slow infusion over 5 minutes 10 minutes before incision.
Outcomes	Blood loss, incidence of PPH (blood loss > 400 ml), vital signs, uterine contractility, placental separation, neonatal manifestations, side effects.
Notes	No placebo was used. Women in both control and study groups received 10 units of oxytocin intravenously and 20 units of oxytocin into the intrauterine wall. The same surgical team performed caesarean section in each hospital.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised consecutive numbered chart.
Allocation concealment (selection bias)	Unclear risk	Unclear.
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The data seem complete.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Yang 2001

Methods	Randomised controlled trial.
Participants	400 primiparous women with term singleton pregnancy, vertex presentation, spontaneous delivery. Had 10 units of oxytocin injected immediately post delivery. Tranexamic acid was given intravenously 2 to 3 minutes after the delivery.

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Yang 2001 *(Continued)*

Interventions	4 groups: I - tranexamic acid 1 g intravenously (n = 94), II - tranexamic acid 0.5 g intravenously (n = 92), III - aminomethylbenzoic acid 0.5 g intravenously (n = 92), IV - no treatment (n = 87).
Outcomes	Incidence of PPH, average blood loss, side effects.
Notes	Aminomethylbenzoic acid is an antifibrinolytic. There was no placebo used. Not blinded.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomly assigned to 4 groups.
Allocation concealment (selection bias)	Unclear risk	It was not mentioned.
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Authors did not mention incomplete data. 35 cases of fetal macrosomia (> 4000 g) were excluded from the study.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	Women who were primipara with term singleton pregnancy, vertex presentation, spontaneous delivery, normal antenatal care, no antepartum haemorrhage, no above moderate PIH, no polyhydramnios, no abnormal birth process or other complications were enrolled in the 2nd stage of labour.

IV: intravenously
PIH: pregnancy-induced hypertension
PPH: postpartum haemorrhage

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

Study	Reason for exclusion
Gobbur 2011	This study was published only in abstract form. The randomisation and allocation concealment were not described. This study reported decreased blood loss in 50 women who received 1 g of tranexamic acid intravenously 20 minutes prior to Caesarean section, in comparison to 50 women who did not receive the drug. No side effects were reported in either group.
Gohel 2007	This was a quasi-randomised trial (randomisation by the rule of odds and even). This study reported decreased blood loss in 50 women who received 1 g of tranexamic acid intravenously 20 minutes prior to Caesarean section, in comparison to 50 women who did not receive the drug. No side effects were reported in either group.
Sekhavat 2009	This was a quasi-randomised trial (randomisation by the rule of odds and even). This study reported decreased blood loss from the end of Caesarean section till 2 hours postpartum in 45 women who received 1 g of tranexamic acid intravenously 10 minutes prior to Cesarean section, in comparison to 45 women who did not receive the drug. Haemoglobin level was significantly greater in tranexamic acid group. No side effects were reported in either group.

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DATA AND ANALYSES

Comparison 1. Tranexamic acid versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Blood loss > 400 ml	2	453	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.36, 0.72]
1.1 Tranexamic acid in vaginal birth	1	273	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.22, 0.68]
1.2 Tranexamic acid in caesarean section	1	180	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.39, 0.96]
2 Blood loss (ml)	2	361	Mean Difference (IV, Fixed, 95% CI)	-75.17 [-108.23, -42.12]
2.1 Tranexamic acid in vaginal birth	1	181	Mean Difference (IV, Fixed, 95% CI)	-71.5 [-115.17, -27.83]
2.2 Tranexamic acid in caesarean section	1	180	Mean Difference (IV, Fixed, 95% CI)	-80.10 [-130.68, -29.52]
3 Side effects (nausea and vomiting)	1	181	Risk Ratio (M-H, Fixed, 95% CI)	4.63 [0.23, 95.14]
3.1 Tranexamic acid 1 g	1	181	Risk Ratio (M-H, Fixed, 95% CI)	4.63 [0.23, 95.14]

Comparison 2. Different doses of tranexamic acid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Blood loss > 400 ml	1	186	Risk Ratio (M-H, Fixed, 95% CI)	2.04 [0.80, 5.21]
2 Mean blood loss	1	186	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-41.06, 40.26]

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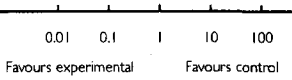
Analysis 1.1. Comparison 1 Tranexamic acid versus placebo/no treatment, Outcome 1 Blood loss > 400 ml.

Review: Tranexamic acid for preventing postpartum haemorrhage

Comparison: 1 Tranexamic acid versus placebo/no treatment

Outcome: 1 Blood loss > 400 ml

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Tranexamic acid in vaginal birth					
Yang 2001	18/186	22/87		45.9 %	0.38 [0.22, 0.68]
Subtotal (95% CI)	**186**	**87**		**45.9 %**	**0.38 [0.22, 0.68]**
Total events: 18 (Experimental), 22 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.31 (P = 0.00093)					
2 Tranexamic acid in caesarean section					
Gai 2004	22/91	35/89		54.1 %	0.61 [0.39, 0.96]
Subtotal (95% CI)	**91**	**89**		**54.1 %**	**0.61 [0.39, 0.96]**
Total events: 22 (Experimental), 35 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.14 (P = 0.033)					
Total (95% CI)	**277**	**176**		**100.0 %**	**0.51 [0.36, 0.72]**
Total events: 40 (Experimental), 57 (Control)					
Heterogeneity: Chi^2 = 1.66, df = 1 (P = 0.20); I^2 =40%					
Test for overall effect: Z = 3.80 (P = 0.00014)					
Test for subgroup differences: Chi^2 = 1.65, df = 1 (P = 0.20), I^2 =39%					



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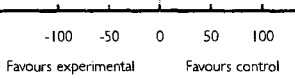
Analysis 1.2. Comparison 1 Tranexamic acid versus placebo/no treatment, Outcome 2 Blood loss (ml).

Review: Tranexamic acid for preventing postpartum haemorrhage

Comparison: 1 Tranexamic acid versus placebo/no treatment

Outcome: 2 Blood loss (ml)

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Tranexamic acid in vaginal birth							
Yang 2001	94	243.3 (106.3)	87	314.8 (180.9)		57.3 %	-71.50 [-115.17, -27.83]
Subtotal (95% CI)	**94**		**87**			**57.3 %**	**-71.50 [-115.17, -27.83]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.21 (P = 0.0013)							
2 Tranexamic acid in caesarean section							
Gai 2004	91	359.3 (152)	89	439.4 (191.5)		42.7 %	-80.10 [-130.68, -29.52]
Subtotal (95% CI)	**91**		**89**			**42.7 %**	**-80.10 [-130.68, -29.52]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.10 (P = 0.0019)							
Total (95% CI)	**185**		**176**			**100.0 %**	**-75.17 [-108.23, -42.12]**
Heterogeneity: Chi^2 = 0.06, df = 1 (P = 0.80); I^2 =0.0%							
Test for overall effect: Z = 4.46 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.06, df = 1 (P = 0.80), I^2 =0.0%							



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Analysis 1.3. Comparison 1 Tranexamic acid versus placebo/no treatment, Outcome 3 Side effects (nausea and vomiting).

Review: Tranexamic acid for preventing postpartum haemorrhage

Comparison: 1 Tranexamic acid versus placebo/no treatment

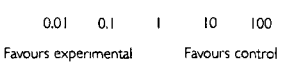
Outcome: 3 Side effects (nausea and vomiting)

Study or subgroup	Tranexamic acid n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Tranexamic acid 1 g					
Yang 2001	2/94	0/87		100.0 %	4.63 [0.23, 95.14]
Total (95% CI)	**94**	**87**		**100.0 %**	**4.63 [0.23, 95.14]**

Total events: 2 (Tranexamic acid), 0 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.99 (P = 0.32)



Analysis 2.1. Comparison 2 Different doses of tranexamic acid, Outcome 1 Blood loss > 400 ml.

Review: Tranexamic acid for preventing postpartum haemorrhage

Comparison: 2 Different doses of tranexamic acid

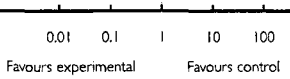
Outcome: 1 Blood loss > 400 ml

Study or subgroup	0.5 G Tranexamic acid n/N	1 G Tranexamic acid n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Yang 2001	12/92	6/94		100.0 %	2.04 [0.80, 5.21]
Total (95% CI)	**92**	**94**		**100.0 %**	**2.04 [0.80, 5.21]**

Total events: 12 (0.5 G Tranexamic acid), 6 (1 G Tranexamic acid)

Heterogeneity: not applicable

Test for overall effect: Z = 1.50 (P = 0.13)



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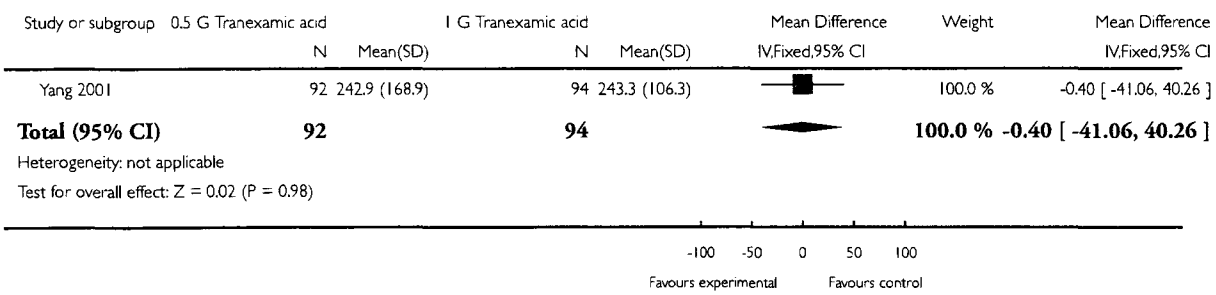
Analysis 2.2. Comparison 2 Different doses of tranexamic acid, Outcome 2 Mean blood loss.

Review: Tranexamic acid for preventing postpartum haemorrhage

Comparison: 2 Different doses of tranexamic acid

Outcome: 2 Mean blood loss



WHAT'S NEW

Last assessed as up-to-date: 11 May 2011.

Date	Event	Description
15 February 2011	New search has been performed	Search updated. We identified and excluded three new trials (Gobbur 2011; Gohel 2007; Sekhavat 2009).

HISTORY

Protocol first published: Issue 3, 2009

Review first published: Issue 7, 2010

CONTRIBUTIONS OF AUTHORS

N Novikova participated in designing the review, and writing the protocol and review. She undertook the initial data analysis. GJ Hofmeyr conceived the review, and provided guidance in designing the review. He also provided a clinical perspective, and performed duplicate data extraction.

For the current update N Novikova assessed the new studies, extracted the data and prepared the first draft of the review. GJ Hofmeyr performed duplicate data extraction and reviewed the drafts of the update.

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DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Effective Care Research Unit, University of Witwatersrand, University of Fort Hare, South Africa, South Africa.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The methods text has been updated to reflect the latest Cochrane *Handbook* (Higgins 2011).

INDEX TERMS

Medical Subject Headings (MeSH)

Aminobenzoic Acids [administration & dosage]; Antifibrinolytic Agents [*administration & dosage]; Injections, Intravenous; Postpartum Hemorrhage [*prevention & control]; Randomized Controlled Trials as Topic; Tranexamic Acid [*administration & dosage]

MeSH check words

Female; Humans; Pregnancy

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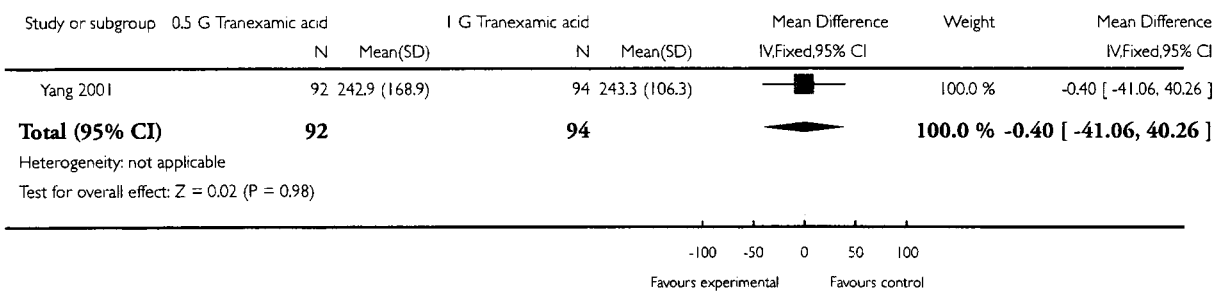
Analysis 2.2. Comparison 2 Different doses of tranexamic acid, Outcome 2 Mean blood loss.

Review: Tranexamic acid for preventing postpartum haemorrhage

Comparison: 2 Different doses of tranexamic acid

Outcome: 2 Mean blood loss



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Misoprostol to prevent and treat postpartum haemorrhage: a systematic review and meta-analysis of maternal deaths and dose-related effects

G Justus Hofmeyr,[a] A Metin Gülmezoglu,[b] Natalia Novikova,[b] Verena Linder,[b] Sandra Ferreira[b] & Gilda Piaggio[a]

Objective To review maternal deaths and the dose-related effects of misoprostol on blood loss and pyrexia in randomized trials of misoprostol use for the prevention or treatment of postpartum haemorrhage.

Methods We searched the Cochrane Controlled Trials Register and Pubmed, without language restrictions, for "(misoprostol AND postpartum) OR (misoprostol AND haemorrhage) OR (misoprostol AND hemorrhage)", and we evaluated reports identified through the Cochrane Pregnancy and Childbirth Group search strategy. Randomized trials comparing misoprostol with either placebo or another uterotonic to prevent or treat postpartum haemorrhage were checked for eligibility. Data were extracted, tabulated and analysed with Reviewer Manager (RevMan) 4.3 software.

Findings We included 46 trials with more than 40 000 participants in the final analysis. Of 11 deaths reported in 5 trials, 8 occurred in women receiving ≥ 600 µg of misoprostol (Peto odds ratio, OR: 2.49; 95% confidence interval, CI: 0.76–8.13). Severe morbidity, defined as the need for major surgery, admission to intensive care, organ failure or body temperature ≥ 40 °C, was relatively infrequent. In prevention trials, severe morbidity was experienced by 16 of 10 281 women on misoprostol and by 16 of 10 292 women on conventional uterotonics; in treatment trials, it was experienced by 1 of 32 women on misoprostol and by 1 of 32 women on conventional uterotonics. Misoprostol recipients experienced more adverse events than placebo recipients: 8 of 2070 versus 5 of 2032, respectively, in prevention trials, and 5 of 196 versus 2 of 202, respectively, in treatment trials. Meta-analysis of direct and adjusted indirect comparisons of the results of randomized trials showed no evidence that 600 µg are more effective than 400 µg for preventing blood loss ≥ 1000 ml (relative risk, RR: 1.02; 95% CI: 0.71–1.48). Pyrexia was more than twice as common among women who received ≥ 600 µg rather than 400 µg of misoprostol (RR: 2.53; 95% CI: 1.78–3.60).

Conclusion Further research is needed to more accurately assess the potential beneficial and harmful effects of misoprostol and to determine the smallest dose that is effective and safe. In this review, 400 µg of misoprostol were found to be safer than ≥ 600 µg and just as effective.

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

Introduction

In low-income countries, postpartum haemorrhage is a major cause of maternal death[1] and arguably the most preventable. Attempts to reduce deaths from postpartum haemorrhage have been complicated by the fact that many deaths occur in out-of-hospital settings or too quickly for the patient to be transferred to a health facility. Furthermore, prevention and treatment have depended primarily on injectable uterotonics, which are seldom available for births outside the health system. For these reasons, the use of misoprostol to prevent or treat postpartum haemorrhage has attracted considerable attention. Misoprostol, an inexpensive and stable prostaglandin E1 analogue, has been shown to stimulate uterine contractility in early pregnancy[2] and at term.[3] Administered orally or vaginally, it is effective for inducing abortion[4,5] and labour,[6–8] though it poses certain risks.[9,10]

Administration of this drug on a wide scale at the community level to prevent and treat postpartum haemorrhage is of major public health importance. The first of many randomized trials of the use of misoprostol in the third stage of labour was conducted in 1995.[11] When administered in various doses and via various routes for the prevention of postpartum haemorrhage, misoprostol has been less effective than conventional injectable uterotonics.[12,13] Initial reports of placebo-controlled trials have shown variable results,[12] but in more recent studies misoprostol has proved better than placebo, in terms of measured blood loss, for both the prevention[14,15] and treatment[16] of postpartum haemorrhage. The main side effects reported have been chills and pyrexia, both of which have been dose-dependent.[17]

We have reviewed the pharmacological, physiological and clinical evidence surrounding the use of misoprostol for the treatment of postpartum haemorrhage.[16] The oral route of administration is the fastest but also the one associated with the shortest duration of action. The rectal route has slow uptake but a prolonged duration of action. The buccal and sublingual routes have rapid intake, prolonged duration of action and the greatest total bioavailability. We concluded from the data reviewed that the most promising route of administration was the sublingual route.

Misoprostol has been widely recommended to prevent postpartum haemorrhage when other methods are not available,[18] and large-scale implementation projects are currently

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(Submitted: 10 June 2008 – Revised version received: 15 November 2008 – Accepted: 25 November 2008 – Published online: 20 July 2009)

in progress. Caution has been urged, however, because side-effects may occasionally be life-threatening.[19] In a recent placebo-controlled trial in rural India in which babies were delivered by auxiliary nurse midwives at home or in village subcentres, a significant reduction in postpartum haemorrhage and other complications was obtained with misoprostol, 600 µg orally used alone (i.e. without other components of the active management of the third stage of labour – umbilical cord clamping and controlled cord traction).[15] WHO has developed guidelines supporting the use of a uterotonic when the full package of active management of the third stage of labour is not practised, which can be either oxytocin, 10 IU administered parenterally, or misoprostol, 600 µg administered orally.[20]

Apart from its uterotonic effects, misoprostol has known pharmacologic effects on several organ systems. It inhibits platelet-activating factor[21] and affects metabolic and physiological processes, including thermoregulation. Life-threatening hyperpyrexia has been reported following the use of misoprostol, 800 µg orally, after childbirth.[22]

Whenever a new medical intervention is promoted, one must take into account not only its clinical benefits and risks, but also the collateral benefits and risks from both use and potential misuse in the community. Before distributing misoprostol at the community level, it is important to consider its possible misuse, an example being its administration before delivery, which could lead to uterine rupture. Because of its enormous potential benefits as an effective, oral uterotonic during the third stage of labour and its likely use on a large scale worldwide, it is important to monitor misoprostol's benefits as well as its potential risks, both direct and indirect.

In September 2005, the *BMJ* published the first placebo-controlled trial to suggest a clear effect of misoprostol for preventing postpartum haemorrhage.[14] The study elicited several responses, however. One of them was the suggestion to regard the single maternal death in the misoprostol group as an adverse event potentially related to misoprostol use.[23] This is plausible because a drug with ubiquitous pharmacologic effects might have unanticipated adverse effects when used in the third stage of labour. Another response was a call for a trial of misoprostol as a treatment for postpartum haemorrhage, with maternal death as the primary endpoint.[24]

In this paper we hypothesized that women on misoprostol in the third stage of labour were at increased risk of death or severe morbidity because of an as yet unexplained adverse effect of the drug on maternal homeostatic functions.[25] Thus, the primary objectives of this review was to investigate maternal deaths and severe morbidity in connection with the use of misoprostol for preventing or treating postpartum haemorrhage during the third stage of labour, as well as to see whether side effects were dose-related. A secondary objective was to determine the relative effectiveness of ≥ 600 µg of misoprostol versus smaller doses, since to justify the use of the larger dose in large numbers of women, particularly in light of potential side effects, would require evidence that it is considerably more effective than the smaller dose.

Methods

Systematic review

Types of studies: We performed a systematic review of randomized controlled trials in which misoprostol versus either placebo or another uterotonic were given to women after delivery to prevent or treat postpartum haemorrhage. We looked for the following primary outcome measures: (i) maternal death, or (ii) maternal death or severe morbidity, defined as either major surgery, admission to the intensive care unit (ICU), vital organ failure or body temperature ≥ 40 °C. For dose comparisons, the outcomes selected were a blood loss of ≥ 1000 ml or of ≥ 500 ml after the diagnosis of postpartum haemorrhage, and pyrexia (i.e. a body temperature ≥ 38 °C or as defined by trial authors).

Search strategy

We followed the search strategy used by the Cochrane Collaboration's Pregnancy and Childbirth Group. Briefly, potentially eligible trials were identified from: (i) quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL); (ii) monthly searches of Medline; (iii) hand searches of 30 journals and the proceedings of major conferences; and (iv) weekly current awareness searches of a further 37 journals. We also searched the Cochrane Controlled Trials Register and Pubmed, without language restrictions, for "(misoprostol AND postpartum) OR (misoprostol AND haemorrhage) OR (misoprostol AND hemorrhage)" (last search February 2007). We tried to contact authors to obtain further details about any maternal deaths reported and, if no maternal death was mentioned in a paper, we asked the authors to confirm that no death had occurred.

All studies identified through the search strategy were assessed for inclusion in the analysis. We designed a data extraction form that was used by two of the authors, and any disagreements were resolved through discussion. We used Review Manager (RevMan) 4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) to enter the data and check it for accuracy.

Assessment of methodological quality

For each trial we classified allocation concealment as follows: (i) adequate if a method such as telephone randomization or consecutively numbered sealed opaque envelopes was used; (ii) unclear if the concealment method was not described; or (iii) inadequate if an open list of random numbers, case record numbers, dates of birth, days of the week or another such method was used.

Measures of treatment effect and assessment of heterogeneity

We used fixed effects meta-analysis for combining data in the absence of significant heterogeneity. For dichotomous data, we presented the results as summary relative risks (RRs) with 95% confidence intervals (CIs). For the outcome maternal mortality, we used both RRs and Peto odds ratios (ORs) to check for discrepancies between the two summary statistics. Peto ORs are recommended when events are very infrequent. We applied tests of heterogeneity between trials using the I^2 statistic, a variation of the χ^2 statistic.

Subgroup analyses

We classified whole trials according to interaction tests as described by Deeks et al.[26] and carried out the following subgroup analyses: (i) misoprostol versus placebo and versus other utero-

tonics; (ii) misoprostol to prevent or treat postpartum haemorrhage; and (iii) misoprostol at a dose of ≥ 600 µg or more; 400 to < 600 µg; or < 400 µg.

In the analysis tables we ranked the trials by route of administration and dose of misoprostol to check for route- or dose-related trends in effects. We coded the trial identifiers to indicate the route of administration and dose used.

Comparisons of dose-related effectiveness and side-effects

In view of inadequate data from direct randomized comparisons of different doses of misoprostol, we supplemented the direct data with adjusted indirect comparisons. In most cases, the results of adjusted indirect comparisons have proved similar to those of direct comparisons in 44 previous meta-analyses.[27] Thus, to estimate the relative effectiveness of two different doses of misoprostol we combined the results of trials in which each dose of the drug was tested against the same type of control (either placebo or a uterotonic other than misoprostol).[28] Three-way comparisons of 600 µg versus 400 µg of misoprostol versus placebo or another uterotonic were included only in the direct comparisons. Studies of rectally-administered misoprostol were excluded because of uncertain absorption via the rectal route.

For direct and indirect comparisons the primary outcome measures were blood loss ≥ 1000 ml and pyrexia ≥ 38 °C. As the effectiveness outcome was blood loss measured within 1 hour of drug administration, doses of misoprostol given 1 hour or more after the initial dose were not taken into account.

Most of the trials in the review were conducted in settings with routine active management of the third stage of labour. To determine if such management affected the results, we performed a sensitivity analysis from which we excluded the one trial in which active management was not practiced.[15]

Prospective adverse-event surveillance studies

We report on adverse events from misoprostol use as recorded in the WHO Adverse Reaction Database, maintained by the Uppsala Monitoring Centre (UMC), which is the WHO Collaborating Centre for International Drug Monitoring. The UMC collects reports of suspected adverse drug reactions from 70 participating countries. We ranked adverse events by frequency of reporting.

Results

Systematic review

We found 46 randomized controlled trials with more than 40 000 participants. They are summarily described in Table 1.

Table 1. **Studies included in a systematic review and meta-analysis of randomized controlled trials of misoprostol for preventing or treating postpartum haemorrhage**

Study[a] [Allocation concealment[b]]	Intervention	Notes
Australia 1999: 400 PO vs U[13]: Not blinded. Randomization by table, in balanced blocks. [A]	M 400 µg PO vs oxytocin (10 IU) or vs oxytocin (5 IU) + ergometrine 0.5 mg IM	3rd stage of labour management not mentioned. Blood loss both estimated and measured.
Belgium 1999: 600 PO vs U[15]: Outcome blinded. Randomization generated by computer; blocks allocation from computer-generated list of study numbers. [A]	M 600 µg PO vs methylergometrine 200 µg IV	Active management of 3rd stage of labour. Blood loss assessment not described.
Canada 2002: 400 PR vs U[29]: Not blinded. Central centre statistician performed block randomization for participating centres. [A]	M 400 µg PR after delivery vs oxytocin 5 IU IV or IM, or 10 IU IM	3rd stage management and blood loss measurement not described.
Canada 2007:400 PO vs U[30]: Not blinded. Randomization generated by computer. [A]	M 400 µg PO vs oxytocin 5 IU IV	Active management of 3rd stage of labour. Blood loss estimated visually and measured.
China 2001: 600 PO vs U[31]: Outcome not blinded. Randomization generated by computer. [A]	M 600 µg PO vs oxytocin 5 IU + ergometrine 0.5 mg IM	Active management of 3rd stage of labour. Blood loss estimated clinically.
China 2004a: 600 SL vs U[32]: Not blinded. Randomization by random numbers table. [C]	M 600 µg SL vs syntocinon 5 IU + ergometrine 0.5 mg IV	Active management of 3rd stage of labour. Blood loss estimated visually and measured.
China 2004b: 400 PO vs P[33]: Double blinded. Randomization generated by computer. [A]	M 400 µg PO vs syntometrine 1 ampoule IM	Management of 3rd stage of labour and blood loss assessment not described.
China 2007: 400 PO vs U[34]: Double blinded. Randomization generated by computer. [A]	M 400 µg PO after delivery vs syntometrine 1 ampoule IM	Active management of 3rd stage of labour. Blood loss estimated clinically.
Colombia 2002: 50 SL vs U[35]: Not blinded. Randomization method not stated. [B]	M 50 µg SL vs oxytocin 16 mIU/min IV vs methylergometrine 0.2 mg IM	Active management of 3rd stage of labour. Blood loss measured.
France 2001: 600 PO vs P vs U[36]: Not blinded. Randomization by drawn envelopes containing treatment codes. [A]	M 600 µg PO vs oxytocin 2.5 IU IV vs no uterotonic	Management of 3rd stage of labour not described. Blood loss measured.
Gambia 2004:600 PO/SL vs P[37]: Blinded. Randomization generated by computer. [A]	M 600 µg PO & SL vs placebo	Active management of 3rd stage of labour. Blood loss measured.

in progress. Caution has been urged, however, because side-effects may occasionally be life-threatening.[19] In a recent placebo-controlled trial in rural India in which babies were delivered by auxiliary nurse midwives at home or in village subcentres, a significant reduction in postpartum haemorrhage and other complications was obtained with misoprostol, 600 µg orally used alone (i.e. without other components of the active management of the third stage of labour – umbilical cord clamping and controlled cord traction).[15] WHO has developed guidelines supporting the use of a uterotonic when the full package of active management of the third stage of labour is not practised, which can be either oxytocin, 10 IU administered parenterally, or misoprostol, 600 µg administered orally.[20]

Apart from its uterotonic effects, misoprostol has known pharmacologic effects on several organ systems. It inhibits platelet-activating factor[21] and affects metabolic and physiological processes, including thermoregulation. Life-threatening hyperpyrexia has been reported following the use of misoprostol, 800 µg orally, after childbirth.[22]

Whenever a new medical intervention is promoted, one must take into account not only its clinical benefits and risks, but also the collateral benefits and risks from both use and potential misuse in the community. Before distributing misoprostol at the community level, it is important to consider its possible misuse, an example being its administration before delivery, which could lead to uterine rupture. Because of its enormous potential benefits as an effective, oral uterotonic during the third stage of labour and its likely use on a large scale worldwide, it is important to monitor misoprostol's benefits as well as its potential risks, both direct and indirect.

In September 2005, the *BMJ* published the first placebo-controlled trial to suggest a clear effect of misoprostol for preventing postpartum haemorrhage.[14] The study elicited several responses, however. One of them was the suggestion to regard the single maternal death in the misoprostol group as an adverse event potentially related to misoprostol use.[23] This is plausible because a drug with ubiquitous pharmacologic effects might have unanticipated adverse effects when used in the third stage of labour. Another response was a call for a trial of misoprostol as a treatment for postpartum haemorrhage, with maternal death as the primary endpoint.[24]

In this paper we hypothesized that women on misoprostol in the third stage of labour were at increased risk of death or severe morbidity because of an as yet unexplained adverse effect of the drug on maternal homeostatic functions.[25] Thus, the primary objectives of this review was to investigate maternal deaths and severe morbidity in connection with the use of misoprostol for preventing or treating postpartum haemorrhage during the third stage of labour, as well as to see whether side effects were dose-related. A secondary objective was to determine the relative effectiveness of ≥ 600 µg of misoprostol versus smaller doses, since to justify the use of the larger dose in large numbers of women, particularly in light of potential side effects, would require evidence that it is considerably more effective than the smaller dose.

Methods

Systematic review

Types of studies: We performed a systematic review of randomized controlled trials in which misoprostol versus either placebo or another uterotonic were given to women after delivery to prevent or treat postpartum haemorrhage. We looked for the following primary outcome measures: (i) maternal death, or (ii) maternal death or severe morbidity, defined as either major surgery, admission to the intensive care unit (ICU), vital organ failure or body temperature ≥ 40 °C. For dose comparisons, the outcomes selected were a blood loss of ≥ 1000 ml or of ≥ 500 ml after the diagnosis of postpartum haemorrhage, and pyrexia (i.e. a body temperature ≥ 38 °C or as defined by trial authors).

Search strategy

We followed the search strategy used by the Cochrane Collaboration's Pregnancy and Childbirth Group. Briefly, potentially eligible trials were identified from: (i) quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL); (ii) monthly searches of Medline; (iii) hand searches of 30 journals and the proceedings of major conferences; and (iv) weekly current awareness searches of a further 37 journals. We also searched the Cochrane Controlled Trials Register and Pubmed, without language restrictions, for "(misoprostol AND postpartum) OR (misoprostol AND haemorrhage) OR (misoprostol AND hemorrhage)" (last search February 2007). We tried to contact authors to obtain further details about any maternal deaths reported and, if no maternal death was mentioned in a paper, we asked the authors to confirm that no death had occurred.

All studies identified through the search strategy were assessed for inclusion in the analysis. We designed a data extraction form that was used by two of the authors, and any disagreements were resolved through discussion. We used Review Manager (RevMan) 4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) to enter the data and check it for accuracy.

Assessment of methodological quality

For each trial we classified allocation concealment as follows: (i) adequate if a method such as telephone randomization or consecutively numbered sealed opaque envelopes was used; (ii) unclear if the concealment method was not described; or (iii) inadequate if an open list of random numbers, case record numbers, dates of birth, days of the week or another such method was used.

Measures of treatment effect and assessment of heterogeneity

We used fixed effects meta-analysis for combining data in the absence of significant heterogeneity. For dichotomous data, we presented the results as summary relative risks (RRs) with 95% confidence intervals (CIs). For the outcome maternal mortality, we used both RRs and Peto odds ratios (ORs) to check for discrepancies between the two summary statistics. Peto ORs are recommended when events are very infrequent. We applied tests of heterogeneity between trials using the I^2 statistic, a variation of the χ^2 statistic.

Subgroup analyses

We classified whole trials according to interaction tests as described by Deeks et al.[26] and carried out the following subgroup analyses: (i) misoprostol versus placebo and versus other utero-

tonics; (ii) misoprostol to prevent or treat postpartum haemorrhage; and (iii) misoprostol at a dose of ≥ 600 µg or more; 400 to < 600 µg; or < 400 µg.

In the analysis tables we ranked the trials by route of administration and dose of misoprostol to check for route- or dose-related trends in effects. We coded the trial identifiers to indicate the route of administration and dose used.

Comparisons of dose-related effectiveness and side-effects

In view of inadequate data from direct randomized comparisons of different doses of misoprostol, we supplemented the direct data with adjusted indirect comparisons. In most cases, the results of adjusted indirect comparisons have proved similar to those of direct comparisons in 44 previous meta-analyses.[27] Thus, to estimate the relative effectiveness of two different doses of misoprostol we combined the results of trials in which each dose of the drug was tested against the same type of control (either placebo or a uterotonic other than misoprostol).[28] Three-way comparisons of 600 µg versus 400 µg of misoprostol versus placebo or another uterotonic were included only in the direct comparisons. Studies of rectally-administered misoprostol were excluded because of uncertain absorption via the rectal route.

For direct and indirect comparisons the primary outcome measures were blood loss ≥ 1000 ml and pyrexia ≥ 38 °C. As the effectiveness outcome was blood loss measured within 1 hour of drug administration, doses of misoprostol given 1 hour or more after the initial dose were not taken into account.

Most of the trials in the review were conducted in settings with routine active management of the third stage of labour. To determine if such management affected the results, we performed a sensitivity analysis from which we excluded the one trial in which active management was not practiced.[15]

Prospective adverse-event surveillance studies

We report on adverse events from misoprostol use as recorded in the WHO Adverse Reaction Database, maintained by the Uppsala Monitoring Centre (UMC), which is the WHO Collaborating Centre for International Drug Monitoring. The UMC collects reports of suspected adverse drug reactions from 70 participating countries. We ranked adverse events by frequency of reporting.

Results

Systematic review

We found 46 randomized controlled trials with more than 40 000 participants. They are summarily described in Table 1.

Table 1. **Studies included in a systematic review and meta-analysis of randomized controlled trials of misoprostol for preventing or treating postpartum haemorrhage**

Study[a] [Allocation concealment[b]]	Intervention	Notes
Australia 1999: 400 PO vs U[13]: Not blinded. Randomization by table, in balanced blocks. [A]	M 400 µg PO vs oxytocin (10 IU) or vs oxytocin (5 IU) + ergometrine 0.5 mg IM	3rd stage of labour management not mentioned. Blood loss both estimated and measured.
Belgium 1999: 600 PO vs U[15]: Outcome blinded. Randomization generated by computer; blocks allocation from computer-generated list of study numbers. [A]	M 600 µg PO vs methylergometrine 200 µg IV	Active management of 3rd stage of labour. Blood loss assessment not described.
Canada 2002: 400 PR vs U[29]: Not blinded. Central centre statistician performed block randomization for participating centres. [A]	M 400 µg PR after delivery vs oxytocin 5 IU IV or IM, or 10 IU IM	3rd stage management and blood loss measurement not described.
Canada 2007:400 PO vs U[30]: Not blinded. Randomization generated by computer. [A]	M 400 µg PO vs oxytocin 5 IU IV	Active management of 3rd stage of labour. Blood loss estimated visually and measured.
China 2001: 600 PO vs U[31]: Outcome not blinded. Randomization generated by computer. [A]	M 600 µg PO vs oxytocin 5 IU + ergometrine 0.5 mg IM	Active management of 3rd stage of labour. Blood loss estimated clinically.
China 2004a: 600 SL vs U[32]: Not blinded. Randomization by random numbers table. [C]	M 600 µg SL vs syntocinon 5 IU + ergometrine 0.5 mg IV	Active management of 3rd stage of labour. Blood loss estimated visually and measured.
China 2004b: 400 PO vs P[33]: Double blinded. Randomization generated by computer. [A]	M 400 µg PO vs syntometrine 1 ampoule IM	Management of 3rd stage of labour and blood loss assessment not described.
China 2007: 400 PO vs U[34]: Double blinded. Randomization generated by computer. [A]	M 400 µg PO after delivery vs syntometrine 1 ampoule IM	Active management of 3rd stage of labour. Blood loss estimated clinically.
Colombia 2002: 50 SL vs U[35]: Not blinded. Randomization method not stated. [B]	M 50 µg SL vs oxytocin 16 mIU/min IV vs methylergometrine 0.2 mg IM	Active management of 3rd stage of labour. Blood loss measured.
France 2001: 600 PO vs P vs U[36]: Not blinded. Randomization by drawn envelopes containing treatment codes. [A]	M 600 µg PO vs oxytocin 2.5 IU IV vs no uterotonic	Management of 3rd stage of labour not described. Blood loss measured.
Gambia 2004:600 PO/SL vs P[37]: Blinded. Randomization generated by computer. [A]	M 600 µg PO & SL vs placebo	Active management of 3rd stage of labour. Blood loss measured.

n concealment[b]]	Intervention	Notes	
PO vs P[36]: Blinded. erated by computer. [A]	M 600 µg PO vs placebo	Active management of 3rd stage of labour. Blood loss measured.	e of labour.
PO vs U[39]: Double blinded. erated by computer. [A]	M 400 µg in powdered form PO (in 50 ml of water) and 1 ml IM injection of normal saline (placebo) vs powdered lactose placebo PO (in 50 ml of water) and 1 ml IM 10 IU oxytocin	Active management of 3rd stage of labour. Blood loss assessment not described.	e of labour. id post-delivery
PR vs U[40]: Not blinded. erated by computer. [A]	M 800 µg PR vs oxytocin 10 IU IM	Management of 3rd stage of labour and blood loss assessment not described.	ion.
5: 600 SL vs P[14,41]: d. Randomization by st. [A]	M 600 µg SL vs identical placebo	Active management of 3rd stage of labour. Blood loss measured.	our and blood
SL vs U[42]: Unclear if outcome blinded. Randomization by ly numbered envelopes. [A]	M 400 µg SL vs methylergometrine 0.2 mg IV	Active management of 3rd stage of labour. Blood loss measured.	
) vs U[43]: Unclear if outcome blinded. Random allocation. B]	M 600 µg PO vs methylergometrine 0.2 mg IV	Active management of 3rd stage of labour. Blood loss assessment not mentioned.	ie of labour.
00 vs SL vs U[44]: Unclear if nts were blinded. erated by computer. [B]	M 400 µg SL vs 20 IU oxytocin in 1 L lactated Ringer's solution at 125 ml/h.	Management of 3rd stage of labour and blood loss assessment not described. All women had Caesarean section with spinal anaesthesia.	
PO vs U[45]: No mention nization generated by	M 400 µg PO vs oxytocin 10 IU IM vs ergometrine 0.2 mg IV	Management of 3rd stage of labour not described. Blood loss measured.	stage of labour.
PO vs P[46]: Blinded. erated by computer. [A]	M 600 µg PO vs identical placebos	Management of 3rd stage of labour not described. Blood loss measured.	age or placental excluded. bour not described.
PR vs U[47]: Interventions omly". [B]	M 400 µg PR vs carboprost 125 µg IM	Management of 3rd stage of labour not described. Blood loss assessed clinically.	
SL vs U[48]: Double blinded. thod not described. [A]	M 400 µg SL vs ergometrine 0.2 mg IM	Management of 3rd stage of labour not described. Blood loss measured.	
PR vs U[49]: Double blinded. erated by computer. [A]	M 600 µg PR vs oxytocin 10 IU IM	Management of 3rd stage of labour not described. Blood loss measured.	or emergency assessed clinically.
00 PO vs U[50]: thod not described. [B]	M 600 µg PO vs oxytocin 10 IU IM	Management of 3rd stage of labour not described. Blood loss measured, method not described.	bour not described.
: 400 PR vs U[51]: ndomization generation cebos prepared daily pendent of the trial and earchers upon request. [B]	M 400 µg dissolved in 5 ml saline PR as a microenema + 1 ml saline placebo IM vs oxytocin 10 IU IM + 5 ml saline microenema (placebo)	Management of 3rd stage of labour not described. Blood loss measured.	ge of labour.
PO vs U[52]: Double blinded. andom number table. [A]	M 600 µg in powder form dissolved in 50 ml water PO vs oxytocin 10 IU IM	Active management of 3rd stage of labour. Blood loss assessed clinically.	an section. "standard"
a: 400 PR vs U[53]: Not blinded. erated by computer. [A]	M 400 µg PR vs ergometrine-oxytocin 1 ampoule IM	Management of 3rd stage of labour not described. Blood loss measured.	
b: 400 PO vs P[11]: ndomization generated by	M 400 µg PO vs placebo	Active management of 3rd stage of labour. Blood loss measured.	ge of labour.
c: 400 PR vs P[54]: Blinded. erated by computer. [A]	M 400 µg PR vs placebo	Active or expectant management of 3rd stage of labour. Blood loss measured.	ge of labour.
d: 600/400 PO vs P[55,56]: ation generated by	M 600 µg PO vs M 400 µg PO vs placebo	Management of 3rd stage of labour not described. Blood loss measured.	bour not described.
a: 600 PO vs P[55]: Blinded. erated by computer. [A]	M 600 µg PO vs placebo	Management of 3rd stage of labour not described. Blood loss measured.	
b: 800 PR vs U[57]: Blinded. erated by computer. [A]	M 800 µg PR vs oxytocin 5 IU IM vs ergometrine 0.5 mg IM	Women with postpartum haemorrhage after vaginal delivery or Caesarean section. Blood loss assessed clinically.	IM = intramuscular;

Table 2. **Maternal deaths and severe morbidity reported in randomized controlled trials of misoprostol to prevent or treat postpartum haemorrhage**

Study[a]	Misoprostol group	Control group
China 2001: 600 PO vs U[71]	No cases	1 hysterectomy in multiparous woman with PPH (5 L) due to uterine atony
China 2004a: 600 PO vs U[52]	PPH (4 L) due to uterine atony in primiparous woman	No cases
Gambia 2004[30]: 600 PO/SL vs P	No cases	2 hysterectomies, no details reported
Gambia 2005[38]: 600 PO vs P	1 maternal death from PPH (2.2 L) in gravida 7, para 6, delivered at home	1 hospital admission for PPH and clinical anaemia
	1 maternal death from disseminated intravascular coagulation due to malaria	2 hospital admissions for severe postpartum anaemia
	2 hospital admissions from severe postpartum anaemia	
Guinea-Bissau 2005[14,41]: 600 SL vs P	1 maternal death, PPH (1.4 L), cause of death not established on autopsy	No cases
India 2006c[54]: 600 PO vs P	2 ICU admissions	2 ICU admissions
South Africa 2001a[55]: 600 PO vs P	1 case of fever > 40 °C	No cases
South Africa 2001b[37]: 80 PO vs U	1 internal iliac artery ligation for severe PPH	1 hysterectomy for severe PPH
South Africa 2004[56]: 1000 PO/SL/PR vs P	1 maternal death from severe PPH, coagulopathy, had hysterectomy, died on day 2 postpartum	No cases
	1 maternal death from severe PPH (3 L) secondary to cervical tear, coagulopathy	
	1 maternal death from PPH (1 L), hypotension and cardiac arrest, possibly had internal bleeding from dehisced Caesarean section scar	
	2 hysterectomies for PPH	
WHO 2001[69,70]: 600 PO vs U	2 maternal deaths	2 maternal deaths
	4 hysterectomies	8 hysterectomies
	4 ICU admissions	5 ICU admissions
	5 cases of fever > 40 °C	

ICU, intensive care unit; IV, intravascular; PPH, postpartum haemorrhage.

[a] The format used for study identifiers was as follows: country, year, misoprostol (M) dose in micrograms (μ), route of administration (IM = intramuscular; IV = intravenous; PO = oral; PR = rectal; SL = sublingual), misoprostol compared with (vs) placebo (P) or another uterotonic (U).

Maternal deaths

Maternal deaths were reported in five trials.[14,15,38,58,69] Three other trials specified that there were no maternal deaths.[30,39,71] No additional maternal deaths were identified through communication with the authors of the included trials.

Fig. 1 (available at: http://www.who.int/bulletin/volumes/87/9/08-055715/en/index.html) shows only the five trials in which maternal deaths were reported. Of 11 deaths reported in these trials,[14,15,38,58,69] 8 occurred in women receiving misoprostol (RR: 2.0; 95% CI: 0.68–5.83; Peto OR: 2.49; 95% CI: 0.76–8.13). Of 8 maternal deaths reported in the misoprostol group, 6 were associated with postpartum haemorrhage.[14,38,58]

Severe maternal morbidity

Fig. 2 (available at: http://www.who.int/bulletin/volumes/87/9/08-055715/en/index.html) shows the data on maternal deaths and severe morbidity as reported in the randomized controlled trials of misoprostol compared with placebo or other uterotonics to prevent or treat postpartum haemorrhage. When misoprostol was compared with other uterotonics, a similar number of adverse events was reported in both prevention and treatment trials: in prevention trials, 16 of 10281 versus 16 of 10292 women, respectively (RR: 1.0; 95% CI: 0.51–1.96); in treatment trials, 1 of 32 women in the treatment as well as the control group (RR: 1.0; 95% CI: 0.07–15.30). When misoprostol was compared with placebo, slightly more adverse events were reported in the misoprostol group in both prevention and treatment trials: in prevention trials, 8 of 2070 versus 5 of 2032 women, respectively (RR: 1.46; 95% CI: 0.52–4.09); in treatment trials, 5 of 196 versus 2 of 202 women, respectively (RR: 2.06; 95% CI: 0.52–8.17). Events were too few to draw any conclusions.

Table 2 presents descriptions of cases of maternal death and morbidity reported in the trials. In a study from India,[15] one maternal death in the placebo group was not related to haemorrhage. In the WHO (2001) study,[69] the causes of two deaths in the injectable uterotonic group were not mentioned. A few studies reported admission of the participants to the ICU. One of them was the WHO

(2001) study, in which 9 women were admitted to the ICU: 4 of 9224 in the misoprostol group and 5 of 9231 in the injectable uterotonic group (RR: 0.80; 95% CI: 0.22–2.98).[69] In a recent study from India, 4 participants were admitted to the ICU: 2 of 812 in the misoprostol group and 2 of 808 in the placebo group.[15]

Blood loss ≥ 1000 ml

In the initial analysis of misoprostol versus placebo (Fig. 3, available at: http://www.who.int/bulletin/volumes/87/9/08-055715/en/index.html), significant heterogeneity (I^2: > 50%) was noted in the results for 600 µg (4914 women; RR: 0.92; 95% CI: 0.54–1.57; I^2: 66%) and for 400 µg (3039 women; RR: 0.80; 95% CI: 0.47–1.37, random effects model; I^2: 58%). The heterogeneity could not be accounted for by route of administration or trial quality. Rather, it appeared to be related to a single outlier study that contributed data to both subgroups. Removal of this study from the meta-analysis eliminated the significant heterogeneity (I^2: < 50%). After exclusion of the outlier, less blood loss ≥ 1000 ml was noted with 600 µg of misoprostol (4514 women; RR: 0.77; 95% CI: 0.59–1.00, trend, fixed effects model) and with 400 µg of misoprostol (2642 women; RR: 0.63; 95% CI: 0.44–0.91) than with placebo.

In one small trial in which 200 µg of misoprostol were compared with placebo (in addition to an oxytocin infusion in both groups) at Caesarean section, no statistically significant difference in blood loss ≥ 1000 ml was found (misoprostol versus placebo: 352 women; RR: 1.13; 95% CI: 0.66–1.94).

When misoprostol was compared with other uterotonics (Fig. 4, available at: http://www.who.int/bulletin/volumes/87/9/08-055715/en/index.html), results showed no heterogeneity (I^2: 0%). Misoprostol, at a dose of 600 to 800 µg, was less effective than other uterotonics (22 827 women; RR: 1.36; 95% CI: 1.17–1.58). Furthermore, the results obtained with 400–500 µg of misoprostol did not differ significantly from those obtained with 600 µg (9772 women; RR: 1.23; 95% CI: 0.96–1.58), even though the sample size was smaller than for the 600–800 µg doses, the direction of the trend was the same.

In one small trial in which misoprostol at a dose of 50 µg administered sublingually was compared with injectable uterotonics, no significant difference was found (75 women; RR: 0.33; 95% CI: 0.04–2.62).

When given in addition to routine methods of treatment (Fig. 5, available at: http://www.who.int/bulletin/volumes/87/9/08-055715/en/index.html), 600–1000 µg of misoprostol in split doses orally, sublingually and/or rectally was more effective than placebo at reducing an additional blood loss ≥ 500 ml after postpartum haemorrhage (397 women; RR: 0.57; 95% CI: 0.34–0.96).

Meta-analysis of direct and adjusted indirect data from randomized trials showed no evidence of a benefit of 600 µg over 400 µg of misoprostol for reducing blood loss ≥ 1000 ml (RR: 1.02; 95% CI: 0.71–1.48; Table 3 and Fig. 6, available at: http://www.who.int/bulletin/volumes/87/9/08-055715/en/index.html). A sensitivity analysis excluding the one trial in which active management was not practised[15] produced similar results (data not shown).

Table 3. **Meta-analysis of direct comparisons and adjusted indirect comparisons of misoprostol, another uterotonic or placebo for risk of PPH**

PPH (≥ 1000 ml of blood)	RR	95% CI
Direct comparison, M, 600 µg vs 400 µg	0.841	0.501–1.411
Indirect adjusted comparison, M, 600 µg or 400 µg, vs P	1.420	0.790–2.555
Indirect adjusted comparison, M, 600 µg or 400 µg, vs U	0.931	0.599–1.446
All	1.023	0.707–1.481

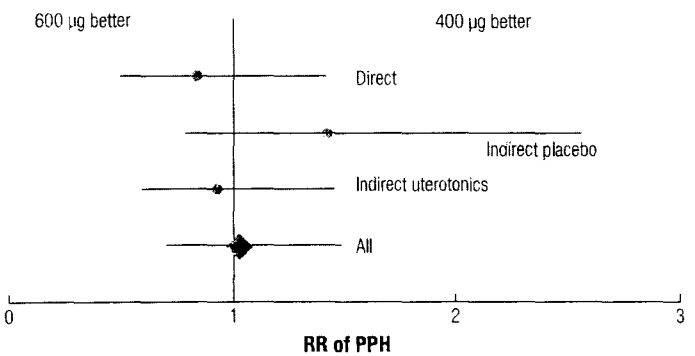
CI, confidence interval; M, misoprostol; P, placebo; PPH, postpartum haemorrhage; RR, relative risk; U, uterotonic besides misoprostol.

Pyrexia

Pyrexia (body temperature ≥ 38 °C or as defined by authors) was higher among women who were given misoprostol in all subgroups (Fig. 7). There was quantitative but not qualitative heterogeneity in the subgroup in which misoprostol, at a dose of 400–500 µg, was compared with other uterotonics (I^2 = 65%). Such heterogeneity could not be explained by route of administration or trial quality.

In comparisons with both placebo and other uterotonics, 600 µg of misoprostol produced pyrexia more often than 400–500 µg: misoprostol, 600 µg versus placebo: 3685 women; RR: 6.71; 95% CI: 4.83–9.32; misoprostol, 400 µg versus placebo: 1996 women; RR: 3.90; 95% CI: 2.27–6,69; misoprostol, 600 µg versus other uterotonics: 22 337 women; RR: 6.76; 95% CI: 5.54–8.25; misoprostol, 400–500 µg versus other

Fig. 7. **Meta-analysis[a] of direct comparisons (misoprostol, 600 µg vs 400 µg) and adjusted indirect comparisons (misoprostol, 600 µg or 400 µg versus another uterotonic or placebo) for risk of PPH**



PPH, postpartum haemorrhage; RR, relative risk.
[a] Each horizontal bar represents the 95% confidence interval.
Graph generated by Review Manager (RevMan) 4.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

uterotonics: 8135 women; RR: 3.05; 95% CI: 2.45–3.81. In the two treatment trials, pyrexia was more common in the misoprostol group (392 women; RR: 2.78; 95% CI: 1.39–5.53).

In meta-analysis of direct and adjusted indirect data from randomized trials, pyrexia was more common in the group given 600 µg of misoprostol rather than 400 µg (RR: 2.53; 95% CI: 1.78–3.60; Table 4 and Fig. 8). There was consistency between the estimates derived from the direct and the adjusted indirect comparisons.

Prospective surveillance of adverse events

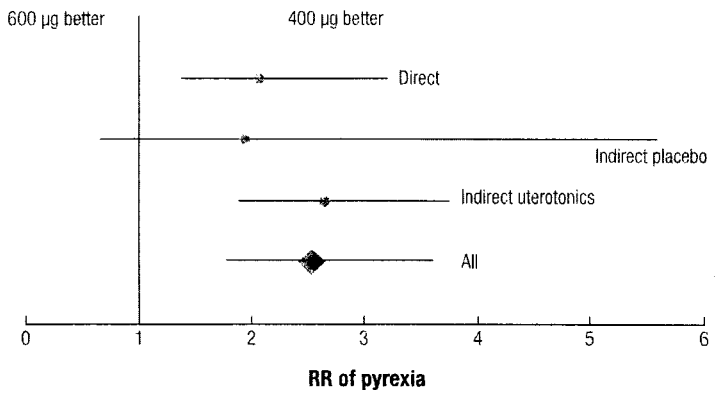
The 14 most frequent adverse events associated with misoprostol use in the WHO Adverse Reaction Database were as follows (an association does not imply causality): diarrhoea (1001), abdominal pain (687), nausea (394), haemorrhage (294), abortion (209), vomiting (209), dyspepsia (162), flatulence (154), dizziness (152), menorrhagia (125), vaginal haemorrhage (153) and fever (98). Death (53) was the 23rd most common adverse event. Without details of the clinical situations in which these complications occurred, it is not possible to draw conclusions from the data.

Table 4. **Meta-analysis of direct comparisons and adjusted indirect comparisons of misoprostol, another uterotonic, or placebo for risk of pyrexia**

Pyrexia (body temperature ≥ 38 °C)	RR	95% CI
Direct comparison, M, 600 µg vs 400 µg	2.059	1.399–3.031
Indirect adjusted comparison, M, 600 µg or 400 µg, vs P	1.944	0.676–5.596
Indirect adjusted comparison, 600 µg or 400 µg, vs U	2.656	1.878–3.758
All	2.532	1.779–3.604

CI, confidence interval; M, misoprostol; P, placebo; RR, relative risk; U, uterotonic besides misoprostol.

Fig. 8. **Meta-analysis[a] of direct comparisons (misoprostol, 600 µg vs 400 µg) and adjusted indirect comparisons (misoprostol, 600 µg or 400 µg versus another uterotonic or placebo) for risk of pyrexia (body temperature [t] ≥ 38 °C or as defined by trial authors)**



RR, relative risk.

[a] Each horizontal bar represents the 95% confidence interval.

Graph generated by Review Manager (RevMan) 4.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Discussion

Misoprostol is used in the third stage of labour primarily to prevent maternal death. Because this is such a rare outcome, no trials to date have been designed to assess the effect on mortality. However, the occurrence of several deaths in misoprostol trials has raised some concern.

It is difficult to evaluate rare adverse outcomes in randomized trials. However, the systematic review of misoprostol trials included in this study provides data on more than 40 000 women. In addition, we complemented our search with adverse events reported to an international centre for such events. To our knowledge, there are no other large population-based datasets or observational studies of maternal deaths or severe adverse outcomes potentially associated with misoprostol use.

Our systematic review of maternal mortality is limited, first, by the small number of deaths associated with misoprostol use and the wide 95% confidence intervals, which are consistent with anything from a modest reduction to a large increase in maternal deaths. Second, this was a post-hoc analysis in response to an observed clustering of maternal deaths, and the statistical calculations need to be interpreted with caution. We recommend prospective surveillance of all randomized trials for further evidence for or against our working hypothesis.

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The cause of death was given for some of the deaths reported in the trials. Some deaths were due to severe haemorrhage, while others did not seem to be directly related to haemorrhage. In addition, deaths were too few to allow for any meaningful interpretation of the role misoprostol or other therapeutic interventions may have played in them.

Although they do not prove our working hypothesis, these results do suggest that misoprostol may have as yet unexplained adverse effects on maternal homeostatic functions in the third stage of labour. The potential for serious side effects is particularly worrisome in connection with the use of misoprostol for preventing, rather than treating, postpartum haemorrhage,

because to prevent a single case of postpartum haemorrhage one would need to treat very large numbers of women.

In estimating the relative effect of 600 µg versus 400 µg of misoprostol on postpartum haemorrhage, we used meta-analysis of direct and adjusted indirect comparisons of randomized trial data to improve the precision of the findings from direct comparisons alone. This method proved useful in an empirical study of 44 meta-analyses.[27] We further validated the method by applying it to the same trials for the outcome pyrexia, for which direct data were reasonably precise because pyrexia was more common than haemorrhage. We found that the findings from adjusted indirect comparisons were consistent with those of direct comparisons.

In all studies in which maternal deaths were reported, misoprostol was given at a dose of ≥ 600 µg. Physiological studies have shown uterotonic effects with doses as low as 200 µg. Our direct and indirect comparisons of data from randomized trials showed no difference in effect size between 600 µg and 400 µg doses. Since misoprostol sometimes produces dose-related side effects such as pyrexia and chills, we suggest that research be undertaken to establish the smallest dose of the drug that is effective and safe.

Because of the enormous benefits of using an effective oral uterotonic in the third stage of labour and since misoprostol could be used in this manner on a large scale worldwide, further research is essential to better assess the potential beneficial and harmful effects of the drug. 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.

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Administration de misoprostol pour prévenir et traiter les hémorragies postpartum : revue systématique et méta-analyse de la mortalité maternelle et des effets dose-dépendants

Objectif Étudier la mortalité maternelle et les effets dose-dépendants du misoprostol sur la perte de sang et la pyrexie dans le cadre d'essais randomisés portant sur l'utilisation de ce médicament pour prévenir et traiter les hémorragies postpartum.

Méthodes Nous avons fait des recherches dans le registre Cochrane des essais contrôlés et dans Pubmed sans émettre de restriction concernant la langue et en utilisant l'expression « (misoprostol AND postpartum) » OR (misoprostol AND haemorrhage) OR (misoprostol AND hemorrhage), puis nous avons évalué les rapports identifiés avec la stratégie de recherche du Groupe Cochrane Pregnancy and Childbirth. Nous avons vérifié la conformité avec les critères d'admissibilité dans l'étude des essais randomisés comparant le misoprostol à un placebo ou à un autre utérotonique dans la prévention ou le traitement des hémorragies postpartum. Nous avons extrait et tabulé des données, puis nous les avons analysées avec le logiciel Reviewer Manager (RevMan) 4.3.

Résultats Dans l'analyse finale, nous avons pris en compte 46 essais portant sur plus de 40 000 participantes. Sur 11 décès rapportés dans 5 essais, 8 sont survenus chez des femmes ayant reçu ≥ 600 µg de misoprostol (Odds ratio de Peto, OR : 2,49 ; intervalle de confiance à 95 %, IC : 0,76-8,13). La morbidité grave, définie comme la nécessité d'une intervention chirurgicale importante, l'admission en soins intensifs, la défaillance d'un organe ou une température corporelle ≥ 40 °C, était relativement rare. Dans les essais de prévention, nous avons relevé une morbidité grave chez 16 des 10281 femmes sous misoprostol et chez 16 des 10292 parturientes recevant un utérotonique classique et, dans les essais thérapeutiques, chez une des 32 femmes sous misoprostol et chez une des 32 femmes sous utérotonique classique. Les femmes recevant du misoprostol ont manifesté plus d'effets indésirables que celles recevant un placebo : 8 sur 2070 contre 5 sur 2032 respectivement dans les essais de prévention et 5 sur 196 contre 2 sur 202 dans les essais thérapeutiques. La méta-analyse des comparaisons directes et indirectes ajustées des résultats d'essais randomisés n'a fait apparaître aucune preuve d'une efficacité supérieure de la dose de 600 µg de misoprostol par rapport à la dose de 400 µg, dans la prévention d'une perte de sang ≥ 1000 ml (risque relatif, RR : 1,02 ; IC à 95 % : 0,71-1,48). La pyrexie était plus de deux fois plus fréquente chez les femmes ayant reçu ≥ 600 µg de misoprostol que chez celles ayant reçu une dose de 400 µg (RR : 2,53 ; IC à 95 % : 1,78-3,60).

Conclusion Des recherches supplémentaires sont nécessaires pour évaluer plus précisément les effets bénéfiques et nocifs potentiels du misoprostol et pour identifier la plus faible dose de ce médicament à la fois efficace et sans risque. La présente étude a trouvé qu'une dose de 400 µg de misoprostol était plus sûre qu'une dose ≥ 600 µg et tout aussi efficace.

uterotonics: 8135 women; RR: 3.05; 95% CI: 2.45–3.81. In the two treatment trials, pyrexia was more common in the misoprostol group (392 women; RR: 2.78; 95% CI: 1.39–5.53).

In meta-analysis of direct and adjusted indirect data from randomized trials, pyrexia was more common in the group given 600 µg of misoprostol rather than 400 µg (RR: 2.53; 95% CI: 1.78–3.60; Table 4 and Fig. 8). There was consistency between the estimates derived from the direct and the adjusted indirect comparisons.

Prospective surveillance of adverse events

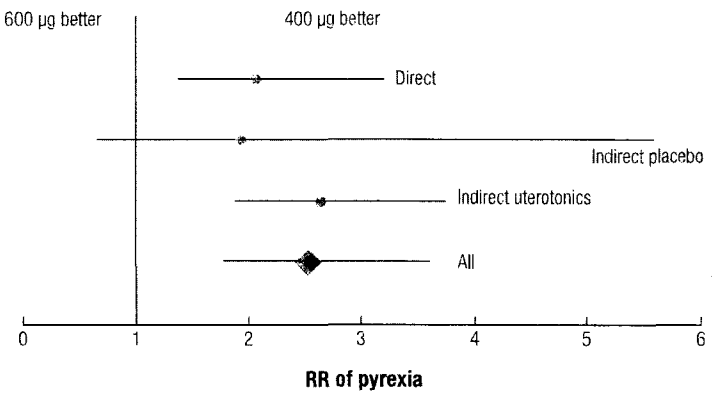
The 14 most frequent adverse events associated with misoprostol use in the WHO Adverse Reaction Database were as follows (an association does not imply causality): diarrhoea (1001), abdominal pain (687), nausea (394), haemorrhage (294), abortion (209), vomiting (209), dyspepsia (162), flatulence (154), dizziness (152), menorrhagia (125), vaginal haemorrhage (153) and fever (98). Death (53) was the 23rd most common adverse event. Without details of the clinical situations in which these complications occurred, it is not possible to draw conclusions from the data.

Table 4. **Meta-analysis of direct comparisons and adjusted indirect comparisons of misoprostol, another uterotonic, or placebo for risk of pyrexia**

Pyrexia (body temperature ≥ 38 °C)	RR	95% CI
Direct comparison, M, 600 µg vs 400 µg	2.059	1.399–3.031
Indirect adjusted comparison, M, 600 µg or 400 µg, vs P	1.944	0.676–5.596
Indirect adjusted comparison, 600 µg or 400 µg, vs U	2.656	1.878–3.758
All	2.532	1.779–3.604

CI, confidence interval; M, misoprostol; P, placebo; RR, relative risk; U, uterotonic besides misoprostol.

Fig. 8. **Meta-analysis[a] of direct comparisons (misoprostol, 600 µg vs 400 µg) and adjusted indirect comparisons (misoprostol, 600 µg or 400 µg versus another uterotonic or placebo) for risk of pyrexia (body temperature [t] ≥ 38 °C or as defined by trial authors)**



RR, relative risk.

[a] Each horizontal bar represents the 95% confidence interval.

Graph generated by Review Manager (RevMan) 4.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Discussion

Misoprostol is used in the third stage of labour primarily to prevent maternal death. Because this is such a rare outcome, no trials to date have been designed to assess the effect on mortality. However, the occurrence of several deaths in misoprostol trials has raised some concern.

It is difficult to evaluate rare adverse outcomes in randomized trials. However, the systematic review of misoprostol trials included in this study provides data on more than 40 000 women. In addition, we complemented our search with adverse events reported to an international centre for such events. To our knowledge, there are no other large population-based datasets or observational studies of maternal deaths or severe adverse outcomes potentially associated with misoprostol use.

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Resumen

Prevención y tratamiento de la hemorragia posparto con misoprostol: revisión sistemática y metanálisis de la mortalidad materna y los efectos dosis-dependientes

Objetivo Analizar la mortalidad materna y los efectos dosis-dependientes del misoprostol sobre la pérdida de sangre y en forma de fiebre en los ensayos aleatorizados realizados sobre su uso con fines de prevención o tratamiento de la hemorragia posparto.

Métodos Utilizamos el Registro de Ensayos Controlados de Cochrane y Pubmed para realizar una búsqueda en todos los idiomas planteada en los siguientes términos: «(misoprostol AND postpartum) OR (misoprostol AND haemorrhage) OR (misoprostol AND hemorrhage)». Se procedió a evaluar los trabajos identificados mediante la estrategia de búsqueda del Grupo Cochrane de Embarazo y Parto, y se determinó la elegibilidad de los ensayos aleatorizados en que se comparó el misoprostol ya fuera con un placebo o con otro uterotónico como forma de prevención o tratamiento de la hemorragia posparto. Los datos extraídos fueron tabulados y analizados con el software Reviewer Manager (RevMan) 4.3.

Resultados Incluimos en el análisis final 46 ensayos que abarcaron a más de 40 000 participantes. De las 11 defunciones notificadas en 5 ensayos, 8 correspondían a mujeres que habían recibido ≥ 600 µg de misoprostol (oportunidad relativa [OR] de Peto: 2,49; intervalo de confianza [IC] del 95%: 0,76–8,13). La morbilidad grave, definida como la necesidad de cirugía mayor, el ingreso en cuidados intensivos, la aparición de insuficiencia orgánica o una temperatura corporal ≥ 40 °C, fue relativamente poco frecuente. En los ensayos de prevención, sufrieron morbilidad grave 16 de las 10 281 mujeres a las que se administró misoprostol, y 16 de las 10 292 mujeres sometidas a uterotónicos convencionales; en los ensayos de tratamiento, sufrieron cuadros graves 1 de 32 mujeres sometidas a misoprostol y 1 de 32 mujeres tratadas con uterotónicos convencionales. Quienes recibieron misoprostol sufrieron más eventos adversos que quienes recibieron placebo: 8 de 2070 frente a 5 de 2032, respectivamente, en los ensayos de prevención, y 5 de 196 frente a 2 de 202, respectivamente, en los ensayos de tratamiento. El metanálisis de las comparaciones directas e indirectas ajustadas de los resultados de los ensayos aleatorizados no aportó ningún indicio de que la dosis de 600 µg sea más eficaz que la de 400 µg para prevenir las hemorragias ≥ 1000 ml (riesgo relativo, RR: 1,02; IC95%: 0,71–1,48). La frecuencia de fiebre entre las mujeres que recibieron ≥ 600 µg de misoprostol fue más del doble que en las tratadas con 400 µg (RR: 2,53; IC95%: 1,78–3,60).

Conclusión Es necesario realizar nuevas investigaciones para evaluar con más precisión los posibles efectos beneficiosos y nocivos del misoprostol y para determinar la dosis más baja eficaz y segura. Según los resultados de este análisis, las dosis de 400 µg de misoprostol son más seguras que las dosis ≥ 600 µg y tienen la misma eficacia.

ملخص

الميزوبروستول للوقاية من النزف التالي للولادة ومعالجته: مراجعة منهجية وتحليل تلوي لوفيات الأمهات وللتأثيرات المتعلقة بالجرعة

الهدف: لمراجعة وفيات الأمهات والتأثيرات المتعلقة بجرعة الميزوبروستول على فقدان الدم وعلى الحمّى في التجارب المعشّاة حول استخدام الميزوبروستول للوقاية من النزف التالي للولادة ومعالجته.

الطريقة: بحث الباحثون في سجل كوكران للتجارب المعشّاة وPubMed، دون أي قيود لغوية، عن كلمات (ميزوبروستول وتال للولادة) أو (ميزوبروستول ونزف) أو (ميزوبروستول ونزف دموي)، وأجروا تقييماً للتقارير التي تعرفوا عليها من خلال استراتيجية البحث في مجموعة كوكران للحمل والولادة. وتحقق الباحثون من التجارب المعشاة التي تقارن بين الميزوبروستول مع دواء غُفْل أو دواء آخر موتّر للرحم بهدف الوقاية من النزف التالي للولادة أو معالجته، من حيث الملاءمة. وقد استخدم الباحثون برنامج إدارة المراجعة (RevMan) بإخراجته الرابعة لاستخلاص المعطيات، وجَدْوَلتها وتحليلها.

الموجودات: ضم التحليل النهائي 46 دراسة شارك فيها ما يزيد على 40 000 مشاركة، ومن بين 11 وفاة أُبلغَ عنها في 5 تجارب، حدثت 8 وفيات لدى نسوة تلقّيْن ما يزيد على 600 مكروغرام من الميزوبروسترول (نسبة الأرجحية لبيتو 2.49، وفاصلة الثقة 95%: 0.76 – 8.13). وكان من النادر نسبياً حصول مراضة وخيمة تعرَّف بأنها تستدعي إجراء جراحة كبرى أو إدخال إلى الرعاية المركّزة، أو فشل أحد الأعضاء، أو ارتفاع درجة حرارة الجسم لأكثر من 40° سيلزيوس. وفي التجارب الخاصة بالوقاية، عانت من مراضة وخيمة، 16 امرأة من بين 281 10 امرأة ممن تلقّيْن الميزوبروستول، و16 امرأة من بين 292 10 تلقّيْن المعالجة التقليدية الموتّرة للرحم. أما في التجارب الخاصة بالمعالجة، فقد عانت من مراضة وخيمة، امرأة واحدة من بين 32 امرأة ممن تلقّيْن الميزوبروستول، وامرأة واحدة من بين 32 امرأة تلقّيْن المعالجة التقليدية. وهكذا عانت النسوة اللاتي تلقين الميزوبروستول من أحداث ضائرة أكثر مما عانت منها النسوة اللاتي تلقّيْن الدواء الغُفل: حيث عانت 8 من بين 2070 من النسوة اللاتي تلقّيْن الميزوبروستول من أحداث ضائرة، وهو أكثر مما عانت منه النساء اللاتي تلقّيْن دواءً غفلاً وهن 5 من أصل 2032؛ وذلك في التجارب الوقائية، أما في تجارب المعالجة، فقد عانت 5 من أصل 196 ممن تلقّيْن الميزوبروستول، من أحداث ضائرة، فيما عانت 2 من أصل 202 ممن تلقّيْن المعالجة بالدواء الغفل. وقد أوضح التحليل التلوي للمقارنات المباشرة والمقارنات غير المباشرة المعدلة لنتائج التجارب المعشّاة عدم وجود بينة على أن إعطاء 600 مكروغرام هو أكثر فعالية من إعطاء 400 مكروغرام للوقاية من فقدان 1000 ميلي لتر أو أكثر من الدم (فالاختطار النسبي 1.02 بفاصلة ثقة 95 %: 0.71 – 1.48). وقد كانت الحمى أكثر شيوعاً لدى من تلقّين أكثر من 600 مكروغرام من الميزوبروستول، بمقدار الضعف مما كانت عليه لدى اللاتي تلقّيْن 400 مكروغرام منه (الاختطار النسبي 2.53، وفاصلة الثقة 95%: 1.78 – 3.60).

الاستنتاج: تمس الحاجة إلى المزيد من البحوث للحصول على تقييم أكثر دقة للتأثيرات المفيدة المحتملة وللتأثيرات الضائرة لاستخدام الميزوبروستول، وللتعرف على الجرعة الأصغر التي تتمتع بالفعالية (النجاعة) والمأمونية. وقد وجد الباحثون في هذه الدراسة أن جرعة مقدارها 400 مكروغرام من الميزوبروستول تعد أكثر مأمونية من جرعة مقدارها 600 مكروغرام منه، رغم أنها تتمتع بنفس القدر من الفعّالية (النجاعة).

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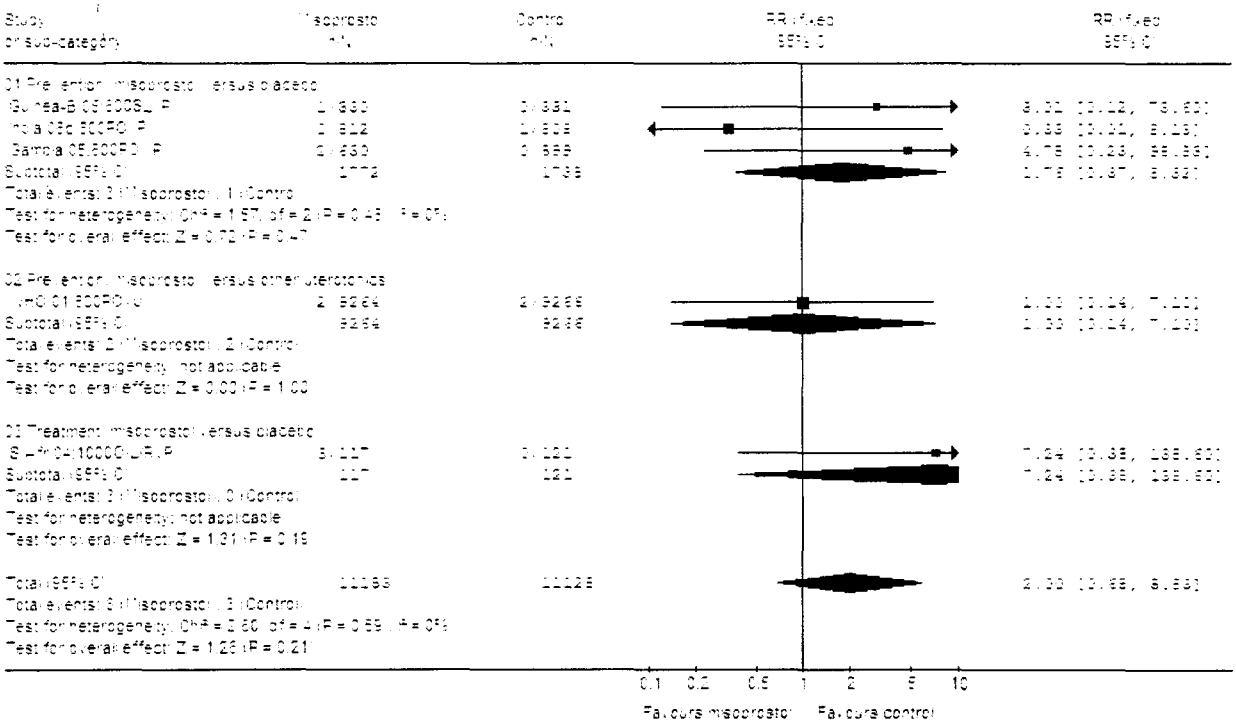
Fig. 1. **Maternal deaths[a] reported in randomized trials of misoprostol[b] versus placebo or another uterotonic to prevent or treat PPH**



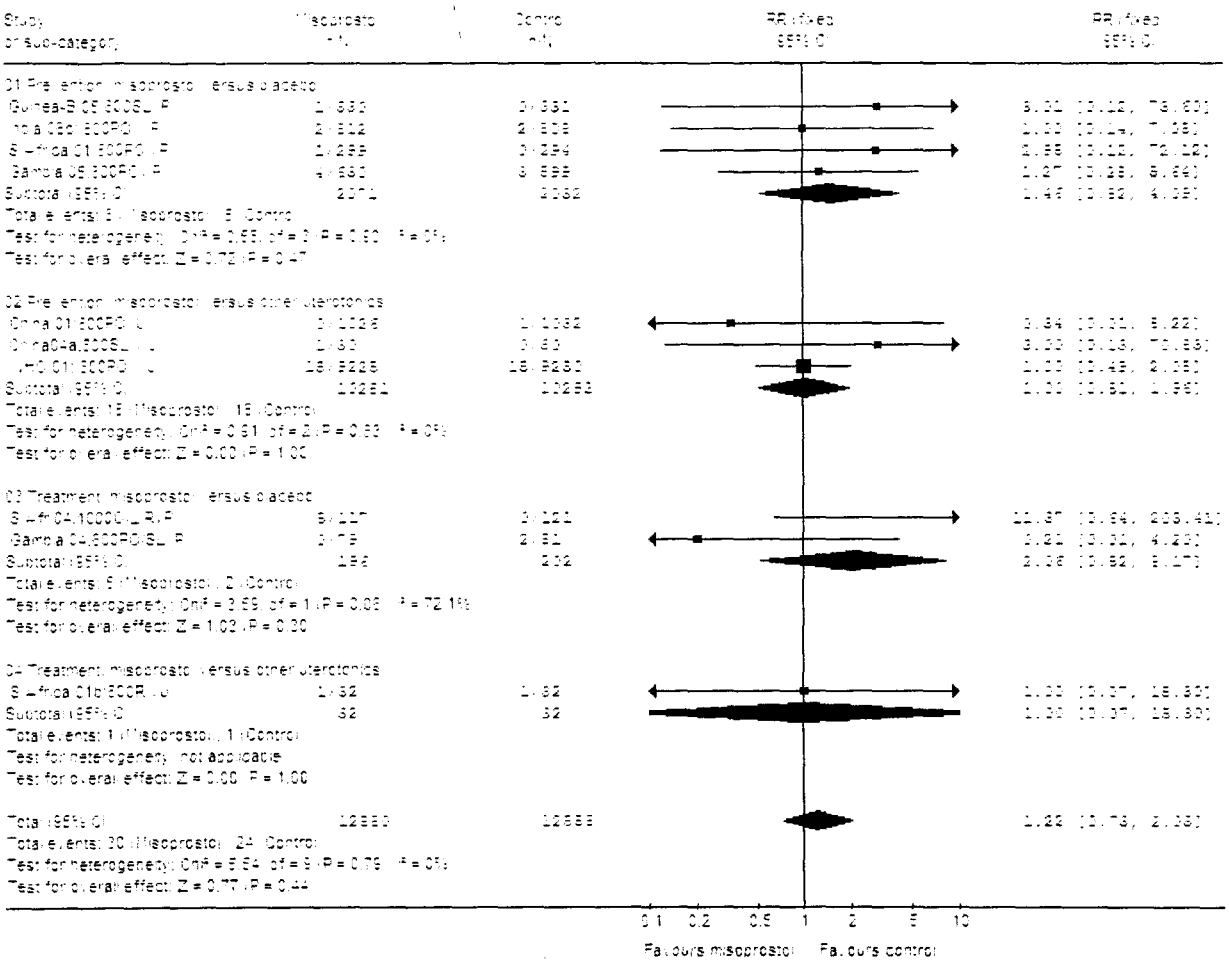
CI, confidence interval; Guinea-B, Guinea-Bissau; L or SL, sublingual; O or PO, oral; P, placebo; PPH, postpartum haemorrhage; R, rectal; RR, relative risk; S Afr, South Africa; U, uterotonic other than misoprostol.

[a] Trials that did not report maternal deaths are not shown. The denominators for all trials are 21 814 for misoprostol groups and 22 526 for control groups. Meta-analysis with all trials included yielded the same RR and 95% CI.

[b] Misoprostol dose always in micrograms.

Graph generated by Review Manager (RevMan) 4.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Fig. 2. **Randomized trials[a] of misoprostol[b] versus placebo or another utrotonic to prevent or treat PPH**



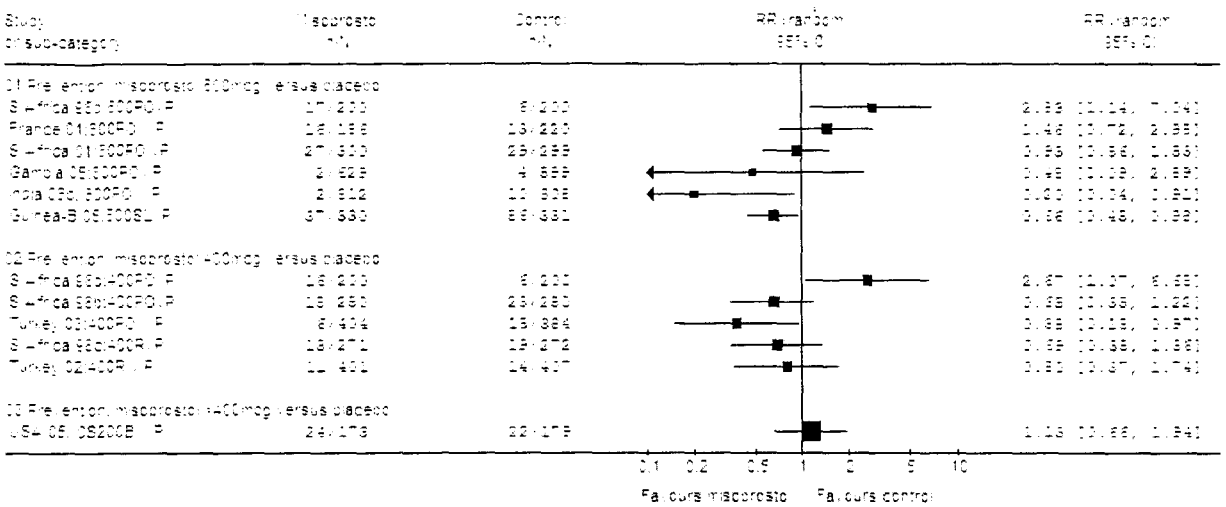
CI, confidence interval; Guinea-B, Guinea-Bissau; L or SL, sublingual, O or PO, oral; P, placebo; PPH, postpartum haemorrhage; R, rectal; RR, relative risk; S Africa, South Africa; U, uterotonic other than misoprostol.

[a] Outcome variables: maternal death or severe morbidity.

[b] Misoprostol dose always in micrograms.

Graph generated by Review Manager (RevMan) 4.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Fig. 3. **Randomized trials of misoprostol[a] versus placebo to prevent PPH, effect on blood loss ≥ 1000 ml**

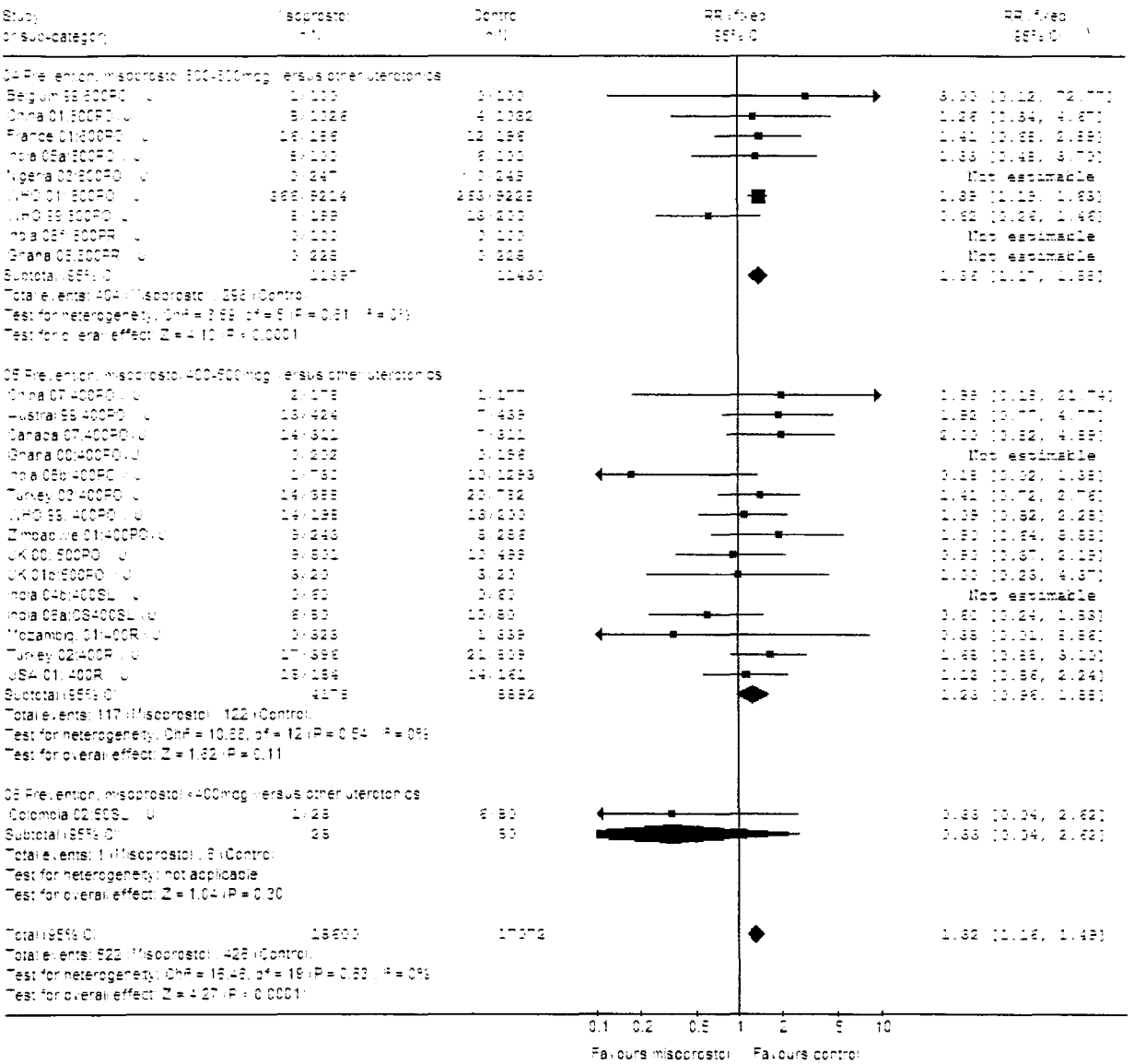


CB, buccal; CI, confidence interval; CS, Caesarean section; SL, sublingual; P, placebo; PO, oral; PPH, postpartum haemorrhage; R, rectal; RR, relative risk; S Africa, South Africa; USA, United States of America.

[a] Misoprostol dose always in micrograms.

Graph generated by Review Manager (RevMan) 4.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

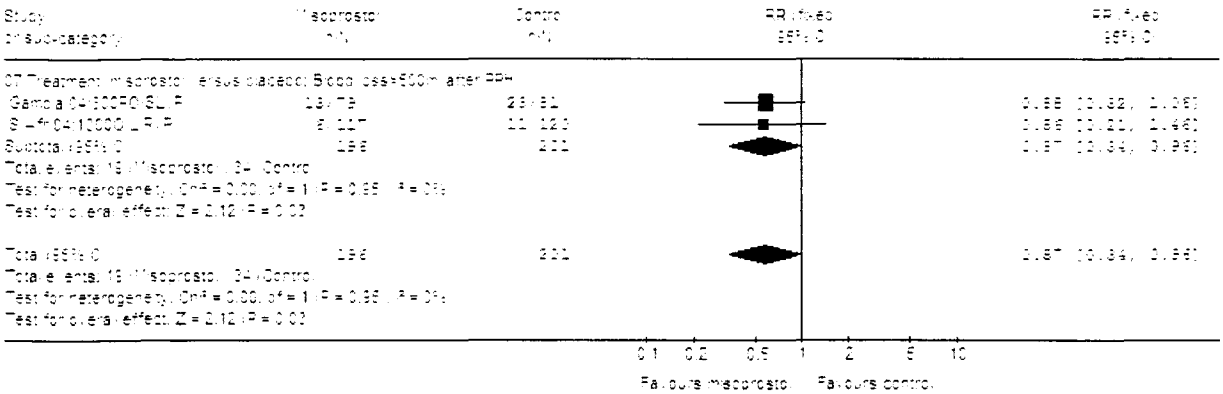
Fig. 4. **Randomized trials of misoprostol[a] versus another uterotonic to prevent PPH, effect on blood loss ≥ 1000 ml**



CI, confidence interval; CS, Caesarean section; PO, oral; PPH, postpartum haemorrhage; R or PR, rectal; RR, relative risk; S Africa, South Africa; SL, sublingual; U, uterotonic other than misoprostol; UK, United Kingdom; USA, United States of America.

[a] Misoprostol dose always in micrograms.

Fig. 5. **Randomized trials of misoprostol[a] versus placebo to treat PPH, effect on additional blood loss ≥ 500 ml following postpartum haemorrhage**

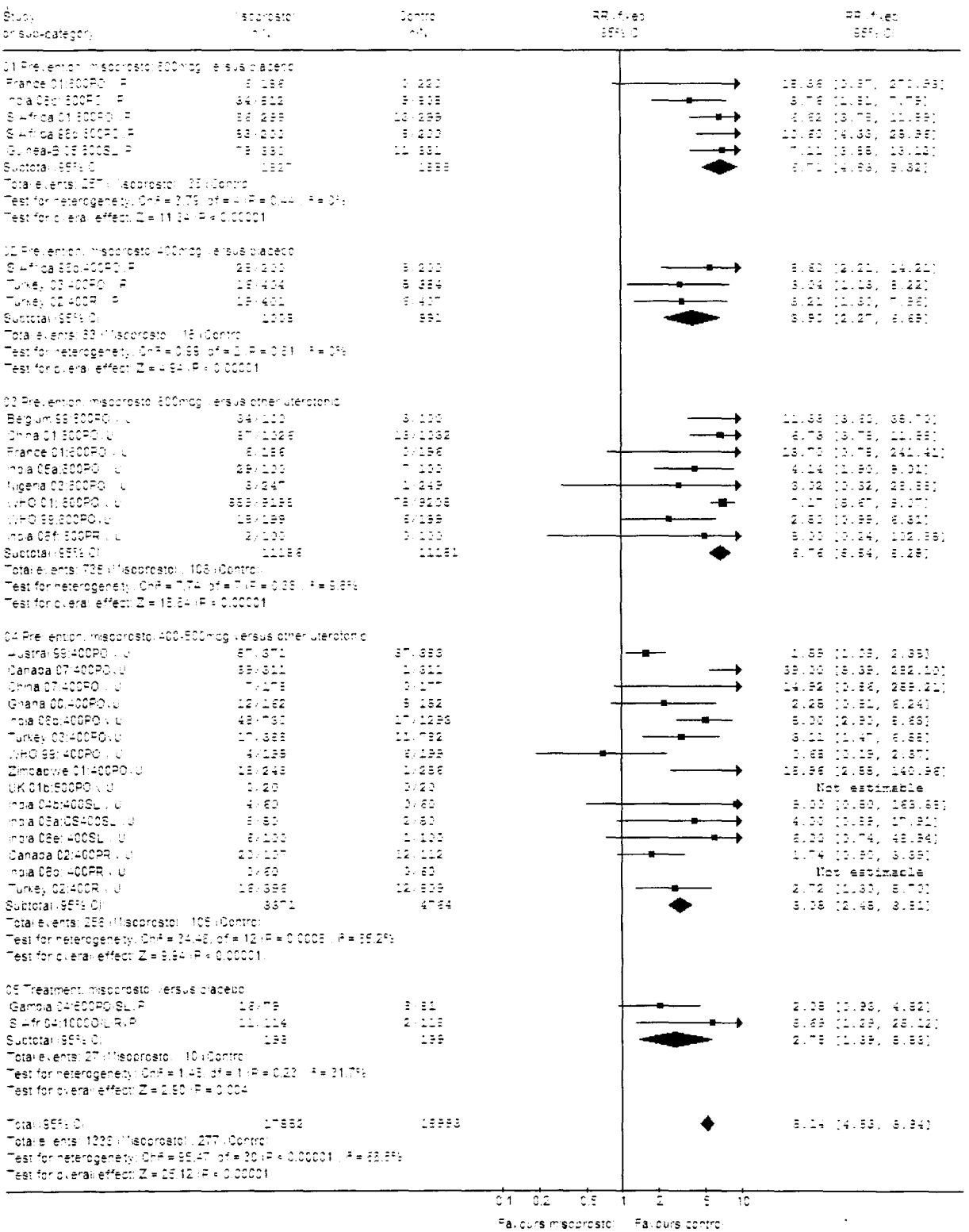


CI, confidence interval; L or SL, sublingual; PO, oral; PPH, postpartum haemorrhage; R, rectal; RR, relative risk; S Africa, South Africa.

[a] Misoprostol dose always in micrograms.

Graph generated by Review Manager (RevMan) 4.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Fig. 6. **Randomized trials of misoprostol[a] versus placebo or another uterotonic to prevent or treat PPH, effect on pyrexia (body temperature [t] ≥ 38 °C or as defined by trial authors[b])**



CI, confidence interval; Guinea-B, Guinea-Bissau; L or SL, sublingual, O or PO, oral; P, placebo; PPH, postpartum haemorrhage; PR or R, rectal; S Afr or S Africa, South Africa; U, uterotonic other than misoprostol; UK, United Kingdom.

[a] Misoprostol dose always in micrograms.

[b] t > 37.1 °C in India 06b; t ≥ 37.3 °C in Australia 99; t ≥ 37.5 °C in Gambia 04 and Ghana 04; t ≥ 37.8 °C in S Africa 98d, 01; t > 37.9 °C in Canada 02; t > 38 °C in Canada 07, Turkey 02, Turkey 03, WHO 99, WHO 01 and Zimbabwe 01; t ≥ 38 °C in Belgium 99, China 01, China 07, France 01, India 04b, India 06f, Guinea-B 05 and Nigeria 03; t ≥ 38.5 °C in S Africa 04; t > 39 °C in France 01; t undefined in India 05a, India 06a, India 06c, India 06d and India 06e.

Graph generated by Review Manager (RevMan) 4.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).