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A B S T R A C T

Background

Postpartum haemorrhage (PPH) is the leading cause of maternal mortality worldwide. Prophylactic uterotonic drugs can prevent PPH, and are routinely recommended. There are several uterotonic drugs for preventing PPH but it is still debatable which drug is best.

Objectives

To identify the most effective uterotonic drug(s) to prevent PPH, and generate a ranking according to their effectiveness and side-effect profile.

Search methods

We searched Cochrane Pregnancy and Childbirth's Trials Register (1 June 2015), ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) for unpublished trial reports (30 June 2015) and reference lists of retrieved studies.

Selection criteria

All randomised controlled comparisons or cluster trials of effectiveness or side-effects of uterotonic drugs for preventing PPH.

Quasi-randomised trials and cross-over trials are not eligible for inclusion in this review.

Data collection and analysis

At least three review authors independently assessed trials for inclusion and risk of bias, extracted data and checked them for accuracy. We estimated the relative effects and rankings for preventing PPH ≥ 500 mL and PPH ≥ 1000 mL as primary outcomes. We performed pairwise meta-analyses and network meta-analysis to determine the relative effects and rankings of all available drugs. We stratified our primary outcomes according to mode of birth, prior risk of PPH, healthcare setting, dosage, regimen and route of drug administration, to detect subgroup effects.The absolute risks in the oxytocin are based on meta-analyses of proportions from the studies included in this review and the risks in the intervention groups were based on the assumed risk in the oxytocin group and the relative effects of the interventions.

Main results

This network meta-analysis included 140 randomised trials with data from 88,947 women. There are two large ongoing studies. The trials were mostly carried out in hospital settings and recruited women who were predominantly more than 37 weeks of gestation having a vaginal birth. The majority of trials were assessed to have uncertain risk of bias due to poor reporting of study design. This primarily impacted on our confidence in comparisons involving carbetocin trials more than other uterotonics.

The three most effective drugs for prevention of PPH ≥ 500 mL were ergometrine plus oxytocin combination, carbetocin, and misoprostol plus oxytocin combination. These three options were more effective at preventing PPH ≥ 500 mL compared with oxytocin, the drug currently recommended by the WHO (ergometrine plus oxytocin risk ratio (RR) 0.69 (95% confidence interval (CI) 0.57 to 0.83), moderate-quality evidence; carbetocin RR 0.72 (95% CI 0.52 to 1.00), very low-quality evidence; misoprostol plus oxytocin RR 0.73 (95% CI 0.60 to 0.90), moderate-quality evidence). Based on these results, about 10.5% women given oxytocin would experience a PPH of ≥ 500 mL compared with 7.2% given ergometrine plus oxytocin combination, 7.6% given carbetocin, and 7.7% given misoprostol plus oxytocin. Oxytocin was ranked fourth with close to 0% cumulative probability of being ranked in the top three for PPH ≥ 500 mL.

The outcomes and rankings for the outcome of PPH ≥ 1000 mL were similar to those of PPH ≥ 500 mL. with the evidence for ergometrine plus oxytocin combination being more effective than oxytocin (RR 0.77 (95% CI 0.61 to 0.95), high-quality evidence) being more certain than that for carbetocin (RR 0.70 (95% CI 0.38 to 1.28), low-quality evidence), or misoprostol plus oxytocin combination (RR 0.90 (95% CI 0.72 to 1.14), moderate-quality evidence)

There were no meaningful differences between all drugs for maternal deaths or severe morbidity as these outcomes were so rare in the included randomised trials.

Two combination regimens had the poorest rankings for side-effects. Specifically, the ergometrine plus oxytocin combination had the higher risk for vomiting (RR 3.10 (95% CI 2.11 to 4.56), high-quality evidence; 1.9% versus 0.6%) and hypertension [RR 1.77 (95% CI 0.55 to 5.66), low-quality evidence; 1.2% versus 0.7%), while the misoprostol plus oxytocin combination had the higher risk for fever (RR 3.18 (95% CI 2.22 to 4.55), moderate-quality evidence; 11.4% versus 3.6%) when compared with oxytocin. Carbetocin had similar risk for side-effects compared with oxytocin although the quality evidence was very low for vomiting and for fever, and was low for hypertension.

Authors' conclusions

Ergometrine plus oxytocin combination, carbetocin, and misoprostol plus oxytocin combination were more effective for preventing PPH ≥ 500 mL than the current standard oxytocin. Ergometrine plus oxytocin combination was more effective for preventing PPH ≥ 1000 mL than oxytocin. Misoprostol plus oxytocin combination evidence is less consistent and may relate to different routes and doses of misoprostol used in the studies. Carbetocin had the most favourable side-effect profile amongst the top three options; however, most carbetocin trials were small and at high risk of bias.

Amongst the 11 ongoing studies listed in this review there are two key studies that will inform a future update of this review. The first is a WHO-led multi-centre study comparing the effectiveness of a room temperature stable carbetocin versus oxytocin (administered intramuscularly) for preventing PPH in women having a vaginal birth. The trial includes around 30,000 women from 10 countries. The other is a UK-based trial recruiting more than 6000 women to a three-arm trial comparing carbetocin, oxytocin and ergometrine plus oxytocin combination. Both trials are expected to report in 2018.

Consultation with our consumer group demonstrated the need for more research into PPH outcomes identified as priorities for women and their families, such as women's views regarding the drugs used, clinical signs of excessive blood loss, neonatal unit admissions and breastfeeding at discharge. To date, trials have rarely investigated these outcomes. Consumers also considered the side-effects of

uterotonic drugs to be important but these were often not reported. A forthcoming set of core outcomes relating to PPH will identify outcomes to prioritise in trial reporting and will inform futures updates of this review. We urge all trialists to consider measuring these outcomes for each drug in all future randomised trials. Lastly, future evidence synthesis research could compare the effects of different dosages and routes of administration for the most effective drugs.

PLAIN LANGUAGE SUMMARY

Which drug is best for reducing excessive blood loss after birth?

What is the issue?

The aim of this Cochrane review was to find out which drug is most effective in preventing excessive blood loss at childbirth and has the least side-effects. We collected and analysed all the relevant studies to answer this question.

Why is this important?

Bleeding after birth is the most common reason why mothers die in childbirth worldwide. Although most healthy women can cope well with some bleeding at childbirth, others do not, and this can pose a serious risk to their health and even life. To reduce excessive bleeding at childbirth, the routine administration of a drug to contract the uterus (uterotonic) has become standard practice across the world. The aim of this research was to identify which drug is most effective in preventing excessive bleeding after childbirth with the least side-effects.

Different drugs given routinely at childbirth have been used for preventing excessive bleeding. They include oxytocin, misoprostol, ergometrine, carbetocin, and combinations of these drugs, each with different effectiveness and side-effects. Some of the side-effects identified include: vomiting, high blood pressure and fever. We analysed all the available evidence to compare all of these drugs and calculated a ranking among them, providing robust effectiveness and side-effect profiles for each drug.

What evidence did we find?

We searched for evidence in June 2015 and found 140 studies involving a total of 88,947 women. The results suggest that an ergometrine plus oxytocin combination, carbetocin, and a misoprostol plus oxytocin combination are the most effective drugs for preventing excessive bleeding after childbirth and are more effective than the drug oxytocin currently recommended by the World Health Organization (WHO). However, ergometrine plus oxytocin and misoprostol plus oxytocin were the worst drugs for side-effects, with carbetocin having the most favourable side-effect profile (less vomiting, high blood pressure and fever). More effective drugs could probably prevent one out of three women from bleeding excessively after childbirth compared to oxytocin. However, existing carbetocin studies were small and of poor quality.

What does this mean?

We found that ergometrine plus oxytocin, misoprostol plus oxytocin, and carbetocin were more effective drugs for reducing excessive bleeding at childbirth than oxytocin which is the current standard drug used to prevent this condition. Carbetocin has the least side-effects among the top three drug options, but to date studies of carbetocin were small and of poor quality.

There are some ongoing studies that are not yet complete, including two key studies. One is a large study (involving around 30,000 women across 10 different countries) comparing the effectiveness of carbetocin versus oxytocin for preventing PPH among women having a vaginal birth. The other is a UK-based trial (involving more than 6000 women) comparing carbetocin, oxytocin and ergometrine plus oxytocin combination. Both trials are expected to report in 2018 and these results will be incorporated when this review is updated.

Consultation with our consumer group has demonstrated a need for more research into PPH outcomes identified as priorities for women and their families, such as women's views regarding the drugs used, clinical signs of excessive blood loss, neonatal unit admissions and breastfeeding at discharge. Trials to date have rarely investigated these outcomes. Consumers also considered the side-effects of uterotonic drugs to be important and these were often not reported. A set of standardised PPH outcomes are being developed and will be incorporated in future updates of this review. We would hope that future trials would also consider adopting those outcomes. Finally, future systematic reviews could compare the effects of different doses and ways of administering the most effective drugs.

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

Effects of uterotonic drugs for preventing postpartum haemorrhage: a network meta-analysis

Patient or population: Women giving birth and at the third stage of labour
Settings: Hospital setting
Intervention: Ergometrine plus oxytocin, Carbetocin, Misoprostol plus oxytocin
Comparison: Oxytocin

Outcomes	Effects and 95% confidence intervals in the effects. Main comparator is oxytocin.				Comments
	Risk with ergometrine plus oxytocin*	**Risk with carbetocin***	**Risk with misoprostol plus oxytocin***	**Risk with oxytocin****	
PPH ≥500 mL	**7.2%** (6 to 8.7) for vaginal births **51.7%** (42.7 to 62.2) for caesareans	**7.6%** (5.5 to 10.5) for vaginal births **53.9%** (38.9 to 74.9) for caesareans	**7.7%** (6.3 to 9.5) for vaginal births **54.7%** (44.9 to 67.4) for caesareans	**10.5%** (9.8 to 11.3) for vaginal births **74.9%** (65.7 to 85.4) for caesareans	There was evidence of global inconsistency in this analysis (P = 0.046). However, the comparisons in this table were consistent except for the comparison of ergometrine versus no treatment not included in this table-based on a single study
	RR 0.69 (0.57 to 0.83) (NMA) RR 0.72 (0.56 to 0.92) (Pairwise)	RR 0.72 (0.52 to 1.00) (NMA) RR 0.69 (0.45 to 1.07) (Pairwise)	RR 0.73 (0.60 to 0.90) (NMA) RR 0.74 (0.62 to 0.88) (Pairwise)	1	
	⊕⊕⊕◯ **moderate** confidence in estimate due to inconsistency based on 10 studies (13,138 women, I^2= 57.4%)	⊕◯◯◯ **very low** confidence in estimate due to risk of bias, imprecision and inconsistency based on 8 studies (917 women, I^2 = 49.9%)	⊕⊕⊕◯ **moderate** confidence in estimate due to inconsistency based on 12 studies (9651 women, I^2 = 60.5%)		
PPH ≥1000 mL	**2.8%** (2.2 to 3.4) for vaginal births **10.7%** (8.5 to 13.2) for caesareans	**2.5%** (1.4 to 4.6) for vaginal births **9.7%** (5.3 to 17.8) for caesareans	**3.2%** (2.6 to 4.1) for vaginal births **12.5%** (10 to 15.8) for caesareans	**3.6%** (3.4 to 3.9) for vaginal births **13.9%** (11.7 to 16.6) for caesareans	There was no evidence of global inconsistency (P = 0.345) in this analysis

	RR 0.77 (0.61 to 0.95) (NMA) RR 0.73 (0.57 to 0.93) (Pair-wise)	RR 0.70 (0.38 to 1.28) (NMA) RR 0.71 (0.38 to 1.35) (Pair-wise)	RR 0.90 (0.72 to 1.14) (NMA) RR 0.89 (0.71 to 1.12) (Pair-wise)	1	
	⊕⊕⊕⊕ **high** confidence in estimate based on 9 studies (13,038 women, I^2 = 0%)	⊕⊕○○ **low** confidence in estimate due to risk of bias and imprecision based on 7 studies (1026 women, I^2 = 0%)	⊕⊕⊕○ **moderate** confidence in estimate due to imprecision based on 14 studies (9897 women, I^2 = 0%)		
Vomiting	**1.9%** (1.3 to 2.7) for vaginal births **16.1%** (11 to 23.7) for cae-sareans	**0.5%** (0.3 to 0.9) for vaginal births **4.6%** (2.9 to 7.4) for cae-sareans	**1.3%** (0.8 to 2) for vaginal births **11.2%** (7.1 to 17.6) for cae-sareans	**0.6%** (0.5 to 0.6) for vaginal births **5.2%** (4.9 to 5.5) for cae-sareans	There was no evidence of global inconsistency (P = 0.06) in this analysis
	RR 3.10 (2.11 to 4.56) (NMA) RR 3.15 (1.72 to 5.78) (Pair-wise)	RR 0.89 (0.55 to 1.42) (NMA) RR 0.88 (0.39 to 1.99) (Pair-wise)	RR 2.16 (1.37 to 3.39) (NMA) RR 2.25 (1.45 to 3.48) (Pair-wise)	1	
	⊕⊕⊕⊕ **high** confidence in estimate based on 8 studies (9811 women, I^2 = 48.1%)	⊕○○○ **very low** confidence in estimate due to risk of bias, inconsistency and imprecision based on 10 studies (1939 women, I^2 = 59.2%)	⊕⊕⊕⊕ **high** confidence in estimate due to imprecision based on 9 studies (5015 women, I^2 = 30.1%)		
Hypertension	**1.2%** (0.4 to 4) for vaginal births **29.6%** (to) for caesareans	**0.6%** (0.1 to 3.3) for vaginal births **14.2%** (2.5 to 79.7) for cae-sareans	Risks not available as no studies report this outcome	**0.7%** (0.7 to 0.8) for vaginal births **16.7%** (11.2 to 24.9) for cae-sareans	There was no evidence of global inconsistency (P = 0.481) in this analysis
	RR 1.77 (0.55 to 5.66) (NMA) RR 0.95 (0.10 to 8.38) (Pair-wise)	RR 0.85 (0.15 to 4.77) (NMA)	RR not available as no studies reported this outcome	1	

	⊕⊕◯◯ **low** confidence in estimate due to inconsistency and imprecision based on 2 studies (1039 women, I^2 = 73.2%)	⊕⊕◯◯ **low** confidence in estimate due to imprecision and based only on indirect evidence	Quality of the evidence cannot be assessed as no studies report this outcome		
Fever	**3%** (1.5 to 6) for vaginal births **11.7%** (6.5 to 23.2) for caesareans	**3.1%** (0.8 to 12.1) for vaginal births **12%** (3.1 to 46.6) for caesareans	**11.4%** (8 to 16.4) for vaginal births **44.2%** (30.9 to 63.2) for caesareans	**3.6%** (3.4 to 3.9) for vaginal births **13.9%** (11.7 to 16.6) for caesareans	There was no evidence of global inconsistency (P = 0. 352) in this analysis
	RR 0.84 (0.42 to 1.67) (NMA) RR 1.07 (0.47 to 2.43) (Pairwise)	RR 0.86 (0.22 to 3.35) (NMA) RR 2.11 (0.18 to 24.40) (Pairwise)	RR 3.18 (2.22 to 4.55) (NMA) RR 2.96 (1.95 to 4.51) (Pairwise)	1	
	⊕⊕⊕◯ **moderate** confidence in estimate due to imprecision based on 2 studies (1591 women, I^2 = 0%)	⊕◯◯◯ **very low** confidence in estimate due to risk of bias, inconsistency and imprecision based on 3 studies (292 women, I^2 = 40.9%)	⊕⊕⊕◯ **moderate** confidence in estimate due to inconsistency based on 15 studies (8209 women, I^2 = 77.8%)		

***The risks in the ergometrine plus oxytocin, carbetocin, misoprostol plus oxytocin groups** (and their 95% confidence interval) are based on the assumed risk in the oxytocin group and the **relative effects** of the interventions (and its 95% CI).

****The risk in the oxytocin group** (and its 95% confidence interval) is based on a meta-analysis of proportions from the studies included in this review for this group.

RR: Risk ratio

GRADE Working Group grades of evidence
High quality:
We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

BACKGROUND

Description of the condition

An estimated 303,000 women died during childbirth in 2015 (Alkema 2016). Postpartum haemorrhage (PPH) accounted for up to a third of all these maternal deaths (Say 2014). Almost all deaths occurred in low- or middle-income countries. Even when death from PPH is avoided, the need for blood transfusion, hysterectomy and additional care place a huge burden on health services (Penney 2007; Souza 2013).

The third stage of labour, defined as the period of time from birth until the delivery of the placenta, and the immediate postpartum period are the most hazardous periods of childbirth due to the risk of PPH. The World Health Organization (WHO) defines PPH as blood loss after birth exceeds 500 mL in the first 24 hours (WHO 2012). Even though healthy women can easily cope with this amount of blood loss, for those who may be malnourished and/or anaemic it can cause considerable morbidity and mortality. The most common cause of PPH is uterine atony (failure of the uterus to contract after delivery), which accounts for 75% of cases (Weekes 1956). Even though risk factors for adverse maternal outcomes from severe haemorrhage have been identified (Souza 2013), often PPH is unpredictable as it occurs in the absence of identifiable clinical or historical risk factors (Combs 1991). Therefore, effective prevention of PPH is advocated for all women during childbirth (WHO 2012). The administration of uterotonic drugs routinely in the third stage of labour is the key intervention that prevents PPH, although there is uncertainty about which drug may be the most effective.

Description of the intervention

The administration of uterotonic drugs to prevent PPH is part of the active management of the third stage of labour, which can prevent two out of three events of PPH (Begley 2015). The active management of the third stage of labour refers to the administration of a uterotonic drug, early cord clamping, and controlled cord traction until delivery of the placenta. The WHO guideline development group recently revisited the evidence underpinning each component of active management of third stage of labour and considered the use of uterotonics as the main intervention within this package (WHO 2012). Uterotonics are also essential for the treatment of PPH, but this is not considered in this review.

How the intervention might work

Several different uterotonic drugs have been used for preventing PPH. These drugs include ergometrine, misoprostol, carbetocin, oxytocin, and the combinations of misoprostol plus oxytocin and ergometrine plus oxytocin.

Oxytocin

Oxytocin (Syntocinon®) is the most widely used uterotonic drug. At low doses, it produces rhythmic uterine contractions that are indistinguishable in frequency, force and duration from those observed during spontaneous labour, but at higher dosages, it causes sustained uterine contractions (MEDICINES.ORG.UK). It has a short half-life, approximately three to five minutes, and can be used as an infusion to maintain uterine contraction. When used intramuscularly, the latent phase lasts two to five minutes, but the uterine activity can last two to three hours (MEDICINES.ORG.UK). However, oxytocin cannot be used orally. It is unstable in ambient temperatures and it requires a cold chain through storage and transport. It should also not be given intravenously as a large bolus, because it can cause severe hypotension (Thomas 2007). Because of its anti-diuretic effect, water intoxication can occur with prolonged infusion of oxytocin (MEDICINES.ORG.UK). Oxytocin has a favourable side-effect profile and it is not significantly worse than placebo for common side-effects such as nausea and vomiting, but the evidence is scarce (Westhoff 2013).

Ergometrine

Ergometrine and methylergometrine are ergot alkaloids that increase the uterine muscle tone by causing sustained uterine contractions. They have a latent phase of two to five minutes after intramuscular injection and the plasma half-life is 30 to 120 minutes (de Groot 1998). However, ergometrine and methylergometrine are unstable in heat with an unpredictable bioavailability, which precludes oral use (de Groot 1996a). They are vasoconstrictive and increase the risk of hypertension postpartum (Liabsuetrakul 2007). Other side-effects with ergot alkaloids are pain after birth, nausea and vomiting (Liabsuetrakul 2007).

Misoprostol

Misoprostol is a prostaglandin E1 analogue, which is licensed for the prevention and treatment of gastric ulcers. It is well known for its off-label use as a uterotonic agent (Tuncalp 2012). It is water-soluble and heat stable (Davies 2001). It is absorbed after nine to 15 minutes after sublingual, oral, vaginal, and rectal use. The half-life is about 20 to 40 minutes. Oral and sublingual routes have the advantage of rapid onset of action, while the vaginal and rectal routes result in prolonged activity and greater bioavailability (Schaff 2005). However, it is associated with side-effects such as diarrhoea, abdominal pain, nausea and vomiting, shivering and pyrexia (Tuncalp 2012).

Carbetocin

Carbetocin is a newer long-acting synthetic analogue of oxytocin with agonist properties. After intravenous injection, it produces sustained uterine contractions within two minutes, lasting for approximately six minutes followed by rhythmic contractions for 60

minutes (Hunter 1992). When carbetocin is administered by an intramuscular injection, the sustained uterine contractions last for approximately 11 minutes and the rhythmic contractions for 120 minutes (Hunter 1992). Carbetocin is heat stable and the side-effect profile appears to be similar to oxytocin (Su 2012).

Combination drugs

The use of combinations of uterotonic drugs is also popular and the most commonly used preparation is ergometrine plus oxytocin (Syntometrine®). This combination is associated with a statistically significant reduction of PPH $\geq$ 500 mL when compared with oxytocin alone, attributable to the additive ergometrine effect (odds ratio (OR) 0.82, 95% confidence interval (CI) 0.71 to 0.95) (McDonald 2004). Another combination is misoprostol plus oxytocin that is also found to be associated with a small reduction in PPH $\geq$ 500 mL (risk ratio (RR) 0.71, 95% CI 0.53 to 0.95) (Tuncalp 2012). However, both these combinations are associated with significant side-effects and despite the difference in PPH $\geq$ 500 mL, there was no difference found for more severe PPH when compared to oxytocin defined as PPH $\geq$ 1000 mL. Hence, the WHO guideline recommends oxytocin over these combinations (WHO 2012).

The WHO recommends that all women giving birth should be offered uterotonics during the third stage of labour for the prevention of PPH; oxytocin (intramuscular/intravenous, 10 international units (IU)) is the uterotonic drug of choice (WHO 2012). Other injectable uterotonics and misoprostol are recommended as alternatives for the prevention of PPH in settings where oxytocin is not available. Carbetocin is found to reduce the need for additional uterotonics (RR 0.62, 95% CI 0.44 to 0.88), but it is more expensive and not better than oxytocin for preventing PPH $\geq$ 1000 mL (WHO 2012).

Why it is important to do this review

Cochrane reviews have compared individual uterotonic agents against another uterotonic agent, placebo or no treatment (Begley 2015; Liabsuetrakul 2007; McDonald 2004; Su 2012; Tuncalp 2012; Westhoff 2013). Such pairwise meta-analyses can only compare two agents that have been compared directly in head-to-head trials (direct evidence). In the absence of a single randomised controlled trial comparing all available uterotonic agents, uncertainty remains over their relative effectiveness and ranking. We conducted a network meta-analysis synthesizing all direct and indirect trial evidence of relative treatment effects in a single coherent analysis for all the competing agents. Indirect evidence is obtained when the relative effectiveness of two competing drugs is inferred through a common comparator, even though this pair may not have been compared directly (Caldwell 2005; Lumley 2002). Our network meta-analysis provides effectiveness and side-effect profiles, along with the ranking for each uterotonic agent.

O B J E C T I V E S

Primary

To identify the most effective uterotonic drug(s) to prevent postpartum haemorrhage (PPH) with a favourable side-effect profile, and to generate a clinically useful ranking of all available uterotonics.

Secondary

To provide the relative effectiveness and side-effect profile of each drug for our primary outcomes within: a) population subgroups (prior risk of PPH, mode of birth and healthcare setting) and b) treatment subgroups (different dosages, routes or regimens of administration of each uterotonic drug).

M E T H O D S

Criteria for considering studies for this review

Types of studies

All randomised controlled comparisons or cluster trials of effectiveness or side-effects of uterotonic drugs for preventing postpartum haemorrhage (PPH) were included. Quasi-randomised trials and cross-over trials were excluded.

Types of participants

The review included studies of pregnant women following a vaginal or caesarean birth in hospital or community settings.

Types of interventions

Trials were eligible if they administered uterotonic agents of any dosage, route or regimen systemically at birth for preventing PPH, and compared them against other uterotonic agents, placebo or no treatment. Trials evaluating uterotonic drugs administered locally or not immediately after birth, or exclusively comparing different dosages, routes or regimens of the same uterotonic agent were excluded. We included trials in which non-pharmacologic co-interventions such as controlled cord traction, cord clamping, or uterine massage was performed as a randomised intervention in all arms of the trial and the effects of such co-interventions were tested through a sensitivity analysis.

We classified drugs into oxytocin, carbetocin, misoprostol, ergometrine (included also ergonovine, methylergonovine), ergometrine plus oxytocin (Syntometrine, oxytocin combined with

ergometrine, ergonovine, or methylergonovine), and misoprostol plus oxytocin. We excluded synthetic prostaglandin analogues of PGF2α (carboprost), and PGE2 (prostin, sulprostone), because these drugs are usually used for *treating* (and not *preventing*) PPH, and are not currently recommended by the WHO as alternatives (WHO 2012).

For this review, we assumed that any woman who meets the inclusion criteria is, in principle, equally likely to be randomised to any of the eligible uterotonic drugs.

Types of outcome measures

We estimated the relative effects and rankings of the competing interventions according to the following outcomes.

Primary outcomes

The primary outcomes of the review were:
1. PPH ≥ 500 mL; and
2. PPH ≥ 1000 mL.

Secondary outcomes

The secondary outcomes of the review were:
1. maternal deaths;
2. maternal deaths or severe morbidity events adapted from WHO "near miss" criteria (WHO 2011) to include major surgery (laparotomy, uterine artery ligation, internal iliac artery ligation, B-Lynch suture, hysterectomy, extensive vaginal repair, admission to the intensive care unit, or vital organ failure (temporary or permanent);
3. additional uterotonics requirement;
4. transfusion requirement;
5. manual removal of the placenta;
6. mean volumes of blood loss (mL);
7. mean durations of the third stage of labour (minutes);
8. change in haemoglobin measurements before and after birth (g/L);
9. clinical signs of excessive blood loss (as defined by the trialists);
10. neonatal unit admission requirement;
11. breastfeeding at discharge; and
12. side-effects such as nausea, vomiting, hypertension, headache, tachycardia, hypotension, abdominal pain, fever and shivering in the first 24 hours postpartum.

Search methods for identification of studies

Electronic searches

We searched Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (1 June 2015). We updated this search on 27 October 2017 and added the results to Studies awaiting classification to be assessed and incorporated at the next update.

The Register is a database containing over 23,000 reports of controlled trials in the field of pregnancy and childbirth. For full search methods used to populate Pregnancy and Childbirth's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings; and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about the Cochrane Pregnancy and Childbirth in the Cochrane Library and select the '*Specialized Register*' section from the options on the left side of the screen.

Briefly, the Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist and contains trials identified from:
1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that has been fully accounted for in the relevant review sections (Included studies; Excluded studies; Studies awaiting classification; Ongoing studies).

In addition, we searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports using the terms given in Appendix 1 (30 June 2015).

Searching other resources

We retrieved additional relevant references cited in papers identified through the above search strategy and we did search for the full texts of trials initially identified as abstracts. We sought information from primary authors to investigate whether these studies met our eligibility criteria, and to obtain outcome and study data. Trials that compared at least two of the drugs were eligible and we searched for all possible comparisons formed by the drugs of interest. We did not apply any language or date restrictions.

Data collection and analysis

Selection of studies

Three review authors retrieved and independently assessed for inclusion all the potential studies we identified (IDG, AM, HW). We resolved any disagreements through discussion or, if required, in consultation with a third person (AC). We created a study flow diagram to map out the number of records identified, included and excluded (Figure 1).

Figure 1.   Study flow diagram.
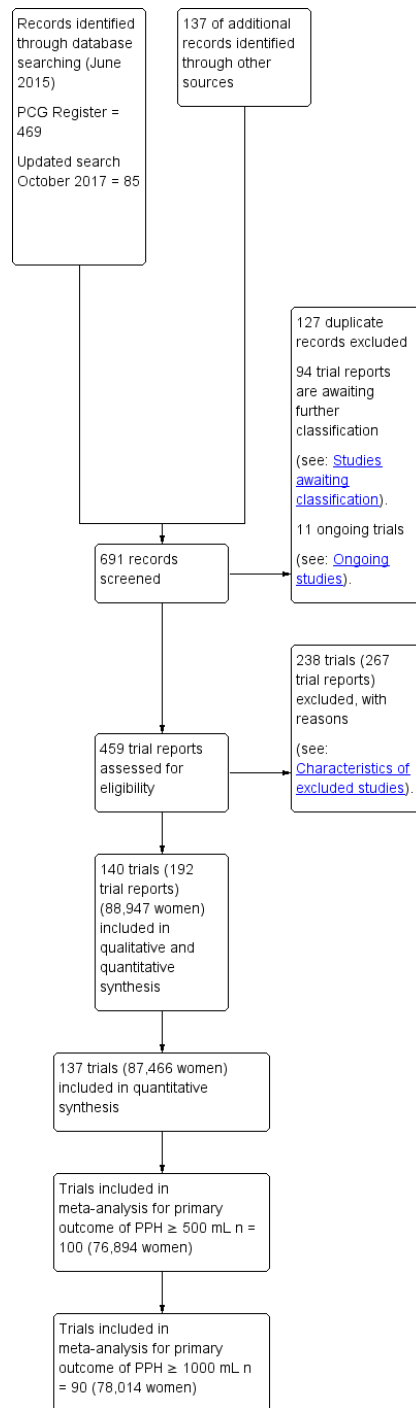
Data extraction and management

We designed an electronic form on ©Microsoft Access to extract data. For eligible studies, at least three review authors independently extracted the data using a blank electronic form (IDG, HW, AM, DL, HG, OT). We resolved discrepancies through discussion or, if required, we consulted another person (AC). We entered data into STATA and Review Manager software (RevMan 2014) and checked for accuracy. When information was unclear, we attempted to contact authors of the original reports to provide further details. The following data were extracted.

Outcome data

From each included study we extracted: the number of participants, the gestational age and the parity of participants, and any exclusion criteria. We also extracted: the interventions being compared, and their respective primary and secondary outcomes. All relevant arm level data were extracted (e.g. number of events and number of patients for binary outcomes).

Data on potential effect modifiers

From each included study we extracted the following study, intervention and population characteristics that may act as effect modifiers:

1. mode of delivery (vaginal or caesarean birth);
2. prior risk of PPH (as defined by trialists and categorised as low, high, mixed or not stated);
3. dosage, regimen, and route of drug administration (sublingual, subcutaneous, intramuscular, rectal, oral, intravenous bolus and/or infusion); and
4. setting of the study (community or hospital).

Other data

From each included study we extracted the following additional information:

1. country or countries in which the study was performed;
2. date of publication;
3. type of publication (full-text publication, abstract publication, unpublished data); and
4. trial registration reference.

Assessment of risk of bias in included studies

At least three (IDG, HW, AM, DL, HG, OT) review authors independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreements were resolved by discussion or by involving another assessor (AC).

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

Studies were excluded if found to be at high risk for bias for random sequence generation (any non-random process, e.g. odd or even date of birth; hospital or clinic record number). We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the methods as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator); or
- unclear risk of bias.

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

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

We assessed the methods as:

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

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

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

We assessed the methods as:

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

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

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received.

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

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

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

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups and less than 10% of missing outcome data);
- 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 or more than 10% of missing outcome data); or
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

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

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

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

We described for each included study any important concerns about other possible sources of bias, such as the source of funding and potential conflicts of interest.
We assessed these interests as:

- low risk of other bias (public funding or no funding and no significant conflicts of interest identified);
- high risk of other bias (industry funding or significant conflicts of interest identified); or

- unclear risk of other bias.

Another source of bias was generated by the method of measuring blood loss. We assessed the method described in each study and classified it as at:

- low risk of other bias (objective measurements such as weighing sponges, measurements in drapes, volumetric assessment, tagged red cells, etc);
- high risk of other bias (subjective measurement such as clinical or visual estimates); or
- unclear risk of other bias (unspecified methods of measurement).

(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 *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to have impacted on the findings. For our primary outcomes, we combined quality items and judged trials as "low risk of bias" if they were double-blinded, had allocation concealment and with little loss to follow-up (less than 10%). Trials were judged as "intermediate risk of bias" if they demonstrated adequate allocation concealment, with assessor blinding and little loss to follow-up (less than 10%). Alternatively, trials were considered to be at "high risk of bias". We explored the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis for information about how the risk of bias was incorporated in the sensitivity analysis.

Summary of findings

A "Summary of findings" table is presented as described by Puhan et al (Puhan 2014). This table shows the overall quality of the body of evidence for the primary review outcomes and important side-effects, using GRADE criteria. GRADE ratings were determined on the basis of risk of bias, inconsistency, indirectness and imprecision. The risks of bias was assessed conventionally for each included trial. A judgement was made to downgrade the quality of the evidence if the majority of the trials for each outcome or each direct comparison were at high risk of bias. The evidence was also downgraded in quality if we found inconsistency between estimates produced by the network meta-analysis and direct estimates obtained from pairwise comparisons. Heterogeneity across studies for each pairwise meta-analysis was assessed using I^2. The evidence was downgraded for indirectness if the included trials for specific direct comparisons were considered to be more restrictive or different than the overall review question. Lastly, evidence was downgraded if there was imprecision. Imprecision relates to the overall level of confidence that may be placed in the estimated

treatment effects. Each quality element considered to have 'serious' or 'very serious' limitations was rated down one or two levels respectively. GRADE assessments were made for the most effective drugs (ergometrine plus oxytocin, carbetocin, and misoprostol plus oxytocin) in comparison with the most frequently used and recommended drug (oxytocin) as a comparison for the primary outcomes and important side-effects. The risk calculated in the comparison group (oxytocin) (and its 95% confidence interval (CI)) was based on a meta-analysis of proportions from the studies included in this review. The risks (and their 95% CIs) calculated in the intervention groups were based on the assumed risk in the comparison group and the relative effects of the interventions (and their 95% CIs). The risks differed significantly by the mode of birth subgroup and they are presented separately for vaginal births and caesareans. Assessments were carried out by IDG and checked by AC.

Measures of treatment effect

Relative treatment effects

We summarised relative treatment effects for dichotomous outcomes as risk ratios (RR) and for continuous outcomes as mean difference (MD) with 95% CIs (Dias 2013).

Relative treatment ranking

We estimated the cumulative probabilities for each treatment being at each possible rank and obtained a treatment hierarchy using the surface under the cumulative ranking curve (SUCRA); the larger the SUCRA the higher its rank among all available drug options (Salanti 2011). The probabilities to rank the treatments are estimated under a Bayesian model with flat priors, assuming that the posterior distribution of the parameter estimates is approximated by a normal distribution with mean and variance equal to the frequentist estimates and variance-covariance matrix (White 2015).

Unit of analysis issues

Cluster-randomised trials

For the only cluster-randomised trial included in this review (Stanton 2013), we used the unadjusted standard errors as the clusters and the Intracluster Correlation Co-efficient (ICC) was small (ICC = 0.012). We considered it reasonable to combine the results from the cluster-randomised and the individually-randomised trials as there was little heterogeneity between the study designs and any interaction between the relative effects of agents and the choice of randomisation unit was considered to be unlikely. The effect of

the unit of randomisation was also assessed in sensitivity analysis (Higgins 2011).

Cross-over trials

This type of trial was not deemed appropriate for this intervention.

Multi-arm trials

Multi-arm trials were included and we accounted for the correlation between the effect estimates in the network meta-analysis. We treated multi-arm studies as multiple independent comparisons in pairwise meta-analyses and these were not combined in any analysis.

Dealing with missing data

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

Assessment of clinical and methodological heterogeneity within treatment comparisons

To evaluate the presence of clinical heterogeneity, we described the study population characteristics across all included trials. We assessed the presence of clinical heterogeneity by comparing these characteristics.

Assessment of transitivity across treatment comparisons

In this context we expect that the transitivity assumption holds assuming the following: 1) the common treatment used to compare different uterotonics indirectly is similar when it appears in different trials (e.g. oxytocin is administered in a similar way in oxytocin versus misoprostol trials and in oxytocin versus oxytocin plus ergometrine trials); 2) all pairwise comparisons do not differ with respect to the distribution of effect modifiers (e.g. the design and study characteristics of oxytocin versus misoprostol trials are similar to oxytocin versus oxytocin plus ergometrine trials). The assumption of transitivity was evaluated epidemiologically by comparing the clinical and methodological characteristics of sets of studies from the various treatment comparisons.

Assessment of reporting biases

We assessed potential reporting bias for the primary outcomes by assessing the sensitivity of results to exclusion of studies with fewer than 400 participants.

Data synthesis

Methods for direct treatment comparisons

Initially, we performed pairwise meta-analyses using a random-effects model in Stata for every treatment comparison with at least two studies (DerSimonian 1986).

Methods for indirect and mixed comparisons

We performed the network meta-analysis within a frequentist framework using multivariate meta-analysis estimated by restricted maximum likelihood. All analyses were done using Stata statistical software, release 14 (StataCorp, College Station, TX). We used the network suite of Stata commands designed from this purpose (White 2012; White 2015).

Assessment of statistical heterogeneity

Assumptions when estimating the heterogeneity

In pairwise meta-analyses we estimated the heterogeneity for each comparison. In network meta-analysis we assumed a common estimate for the heterogeneity variance across all of the different comparisons.

Measures and tests for heterogeneity

We assessed statistically the presence of heterogeneity within each pairwise comparison for the primary outcomes using the I^2 statistic that measures the percentage of variability that cannot be attributed to random error (Higgins 2002). The assessment of statistical heterogeneity in the entire network was based on the magnitude of the heterogeneity variance parameter estimated from the multivariate meta-analysis.

Assessment of statistical inconsistency

To check the assumption of consistency in the entire network we used the "design-by-treatment" interaction model as described by Higgins (Higgins 2012). This method accounts for a different source of inconsistency that can occur when studies with different designs (two-arm trials versus three-arm trials) give different results as well as disagreement between direct and indirect evidence. Using this approach we inferred about the presence of inconsistency from any source in the entire network based on a Chi^2 test.

Investigation of heterogeneity and inconsistency

Where we found important heterogeneity and/or inconsistency, we explored the possible sources for primary outcomes. Where sufficient studies were available, we performed multivariate meta-analyses or subgroup analyses by using the following potential effect modifiers as possible sources of inconsistency and/or heterogeneity.

1. Population: prior risk of PPH (high versus low), mode of delivery (vaginal versus caesarean birth), setting (hospital versus community).
2. Intervention: dose of misoprostol ($\geq$ 600 mcg versus < 600 mcg), and regimen of oxytocin (bolus versus bolus plus infusion versus infusion only).
3. Risk of bias of the studies: studies are ranked as "low risk of bias" if they are double-blinded, and have allocation concealment with little loss to follow-up (less than 10%). The concealed studies with assessor blinding and little loss to follow-up (less than 10%) are ranked as "intermediate risk of bias" and the rest as "high risk of bias". We considered that assessor blinding was likely to be very important, in order to eliminate any risk of bias in subjective measurements or estimates of blood loss (not all studies measure this outcome objectively). We considered protocol publication in advance of the results to be an unsuitable criterion for sensitivity analyses, because protocol publication only became widespread in recent years.
4. Funding source (high versus low risk of bias).
5. Whether an objective method of outcome assessment was employed (objective versus subjective). Objective methods of blood loss measurement were considered to be all methods that employed a measurement of the blood loss. This is in contrast to subjective methods where a healthcare professional is estimating the blood loss, usually visually.
6. Trial size (excluding small studies, in recognition of the greater likelihood for small studies than large or multi-centre studies to suffer publication bias). In terms of trial size, there is evidence that smaller studies can exaggerate estimated benefits (Nüesch 2010). However, the cut-off for deciding the definition of a small study can vary between research topics. For this topic, it appears that trials with more than 400 participants are more likely to be of higher quality, prospectively registered and overall at low risk of bias.
7. Randomisation unit (cluster versus individual).

Subgroup analysis

For the primary outcomes we carried out the following subgroup analyses.

1. Population: prior risk of PPH (high versus low), mode of delivery (vaginal versus caesarean birth), setting (hospital versus community).
2. Intervention: dose of misoprostol ($\geq$ 600 mcg versus < 600 mcg), and regimen of oxytocin (bolus versus bolus plus infusion

versus infusion only).

We assessed subgroup differences by firstly comparing the network diagram for each subgroup. Next, we performed a network meta-analysis for each subgroup and we compared their relative treatment effects and their relative treatment ranking..

Sensitivity analysis

For the primary outcomes we performed sensitivity analysis for the following.

1. Risk of bias of the studies as described previously.
2. Funding source as described previously.
3. Whether an objective method of outcome assessment was employed (objective versus subjective).
4. Trial size as described previously.
5. Trials that also randomised participants to co-interventions such as uterine massage or controlled cord traction.
6. Trials with more than 10% missing data.
7. Trials published before 1990.
8. Randomisation unit (cluster versus individual).
9. Choice of relative effect measure (RR versus OR).
10. Use of fixed-effect versus random-effects model.

Differences were assessed by evaluating the relative effects and assessment of model fit.

R E S U L T S

Description of studies

Results of the search

The results of the search strategy are summarised in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Figure 1).

The search of Cochrane Pregnancy and Childbirth's (CPC) Trials Register in June 2015 retrieved 469 trial reports. A further 137 records were retrieved from additional author searches and manual searching of reference lists. In October 2017, an updated search of the CPC Register retrieved an additional 85 trial reports. After exclusion of duplicates, we assessed for eligibility 378 trials by full-text evaluation. We have included in this systematic review 140 randomised trials (192 trial reports) involving 88,947 women, From these, 137 trials involving 87,466 women, comparing six active drugs contributed data to the network meta-analysis.

We have contacted the authors from 95 primary randomised trials for additional data or clarifications and were able to add in this review data not reported in the published reports for 40 randomised trials.

We excluded 238 trials (267 trial reports) and 11 trials are ongoing (Ongoing studies). We also have 94 trial reports that are awaiting further classification and we plan to assess these at the next update (see: Studies awaiting classification).

Included studies

Most studies were reported in English; nine translations were obtained (four Spanish, two French, two Turkish and one Chinese). The studies were conducted in various countries and often involved more than one country. The UK was the country where most studies were conducted (11 studies). A number of multi-arm trials were identified: two five-arm trials, six four-arm trials and 15 three-arm trials. The median size of the trials was around 248 participants (interquartile (IQR) 136 to 622).

Most trials (96.4%, 135/140) were performed in a hospital setting with only four community trials (2.9%) and one (0.7%) in a mixed setting. The majority of the trials included women undergoing a vaginal birth (74.3%, 104/140), and 36 trials (25.7%) involved women undergoing elective or emergency caesareans. Women included in the trials were judged to be at high risk for postpartum haemorrhage (PPH) in 43 of 140 trials (30.7%), low risk in 42 trials (30%) and 50 trials (35.7%) included women both at high or low risk for PPH. The risk for PPH was not specified in five trials (3.6%).

The gestational age of women included in the trials was not specified in 70 of 140 trials (50%). Thirty-two trials (22.9%) included women with term pregnancies and the remaining 38 trials (27.1%) included women with both pre-term or term pregnancies. Eighty-two trials (58.6%) included women with a singleton pregnancy, 23 trials (16.4%) included women with either singleton or multiple pregnancies and 35 trials (25%) did not specify this criterion. Four trials (2.9%) included only nulliparous or primigravida women, one trial included only multiparous women (0.7%), 35 trials (25%) included women of all parities and 100 trials (71.4%) did not specify the parity of the women included in the trials. Exclusion criteria varied significantly and usually encompassed women with significant medical comorbidities. See Characteristics of included studies for details.

Excluded studies

We excluded 238 randomised trials (for details *see* Characteristics of excluded studies).

Risk of bias in included studies

We present summaries of the methodological quality of the included studies for each of the domains we assessed across all studies (Figure 2) and for each included study (Figure 3).

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
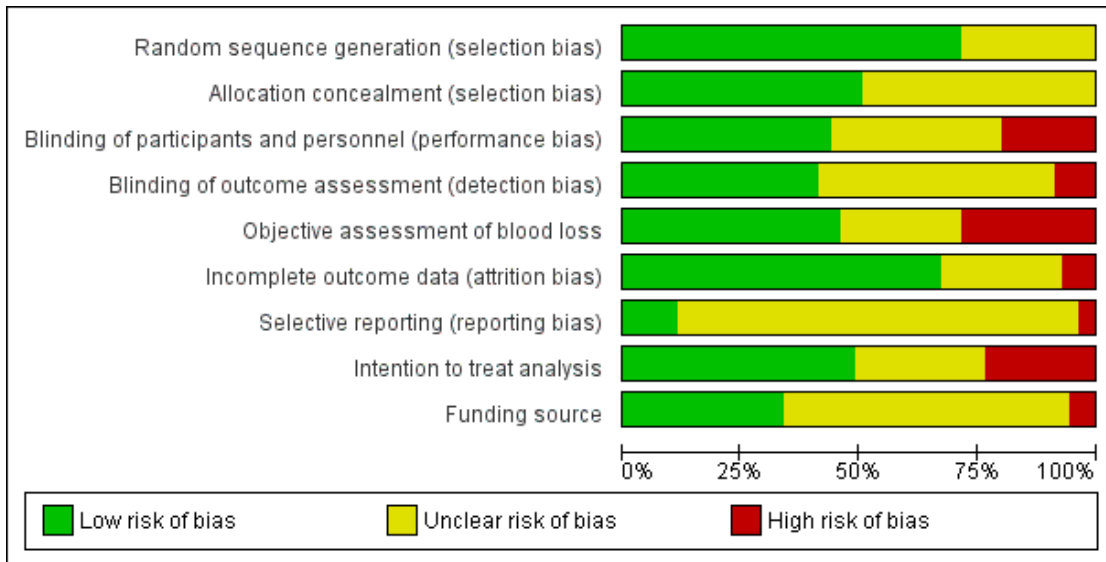
Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

Allocation

Trials with evidence of inadequate random sequence generation were excluded from this review. As a result 100 of 140 included trials (71.4%) were found to have used an adequate method generating the random sequence and were at low risk of bias. However, 40 trials (28.6%) did not report the method used in sufficient detail and the risk of bias was judged to be unclear. Seventy-one of 140 trials (50.7%) reported adequate methods for allocation concealment and were judged to be at low risk of bias. Sixty-nine trials (49.3%), did not provide enough information to assess allocation concealment and the risk of bias was judged to be unclear.

Blinding

In total, 61 of 140 trials (43.6%) reported adequate methods for blinding both participants and personnel to treatment allocation. Twenty-eight trials (20.0%) were judged to be at high risk of bias for blinding of participants and personnel. Fifty-one trials (36.4%) did not provide enough information to assess the blinding of participants and personnel and the risk of bias was judged to be unclear. Fifty-eight of 140 trials (41.47%) reported adequate methods for blinding the assessment of the primary outcomes. Twelve trials (8.6%) were judged to be at high risk of bias for blinding the assessment of the primary outcomes. Seventy trials (50.0%) did not provide enough information for blinding the assessment of the primary outcomes and the risk of bias was judged to be unclear.

Incomplete outcome data

Ninety-four of 140 trials (67.1%) were judged to be at a low risk of bias. In these trials, missing outcome data were less than 10% and balanced in numbers across intervention groups with similar reasons for missing data across groups. In 10 trials (7.1%), more than 10% of patients dropped out or were not analysed as per the "intention-to-treat" principles following randomisation, indicating a high risk of bias. Thirty-six trials (25.7%) did not provide enough information to assess so that it was uncertain whether or not the handling of incomplete data was appropriate and the risk of bias was judged to be unclear in these trials.

Selective reporting

Only 16 of 140 trials (11.4%) pre-specified all outcomes in publicly available study protocols and were judged to be at low risk of bias. Five trials (3.6%) did not report all pre-specified outcomes as reported in their published protocols or methodology within the main report and were judged to be at high risk of bias for selective reporting. For most trials (119 trials; 85.0%), we were unable to trace a published protocol and the risk of bias was judged to be unclear.

Other potential sources of bias

We found that 47 of 140 trials (33.6%) were either conducted with public or no funding and did not declare potential conflicts of interest. Eight trials (5.7%) were judged to be at high risk of bias as they were funded directly by the pharmaceutical industry. Eighty-five trials (60.7%) did not provide enough information to assess the source of funding or potential conflicts of interest and the risk of bias was judged to be unclear.

Among all the studies, 64 of 140 trials (45.7%) reported relatively objective methods for measuring blood loss such as weighing sponges, measurements in drapes or volumetric assessment and were judged to be at low risk of bias. Forty trials (28.6%) were judged to be at high risk of bias for measuring blood loss as they used subjective measurement such as clinical or visual estimates. Thirty-six trials (25.7%) did not measure blood loss or did not provide enough information to assess the method for measuring blood loss, and the risk of bias was judged to be unclear. Three included studies did not report useable blood loss data and were not included in the network meta-analysis (Fawole 2011, Kikutani 2006, Ramirez 2001).

For the purpose of sensitivity analysis we analysed how many trials were judged to be at low, intermediate or high overall risk of bias. For PPH $\geq$ 500 mL, 29 of 100 trials (29%) were found to be at low overall risk of bias. Seventy-one of 100 trials (71%) were judged to be at high risk of bias as they were judged to be either at high risk or unclear risk of bias for at least one of the domains mentioned above. There were no trials judged as intermediate risk of bias - see Sensitivity analysis for information about how this risk of bias has impacted the results.

Effects of interventions

See: **Summary of findings for the main comparison**

Primary outcomes

Postpartum haemorrhage (PPH) $\geq$ 500 mL

The network diagram for PPH $\geq$ 500 mL is presented in Figure 4. Oxytocin was the most frequently investigated uterotonic agent (82%, 82 of 100 trials) (Figure 4).

Figure 4. Network diagram for PPH ≥ 500 mL. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is green when more than 50% of the trials involved in the specific direct comparison are judged to be at "low risk of bias" if they were double-blinded, and had allocation concealment with little loss to follow-up (less than 10%). The colour is red when less than 50% of the trials are at "low risk of bias". Multi-arm trials contribute to more than one comparison.
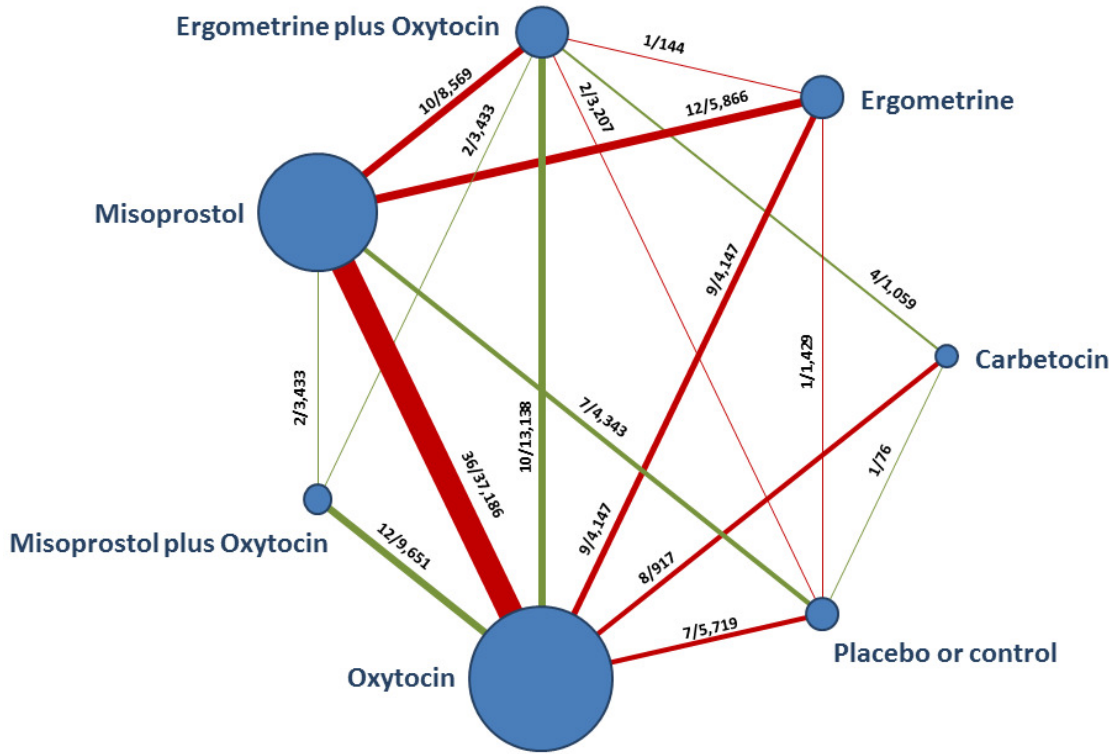
Pooled effect sizes from the network meta-analysis of 100 trials suggested that all drugs were effective for preventing PPH ≥ 500 mL when compared with placebo or no treatment (Figure 5). The three most effective options for prevention of PPH ≥ 500 mL were ergometrine plus oxytocin combination, carbetocin, and misoprostol plus oxytocin combination. All three drugs more effectively reduced the risk of PPH ≥ 500 mL than oxytocin (ergometrine plus oxytocin risk ratio (RR) 0.69 (95% confidence interval (CI) 0.57 to 0.83); carbetocin RR 0.72 (95% CI 0.52 to 1.00); misoprostol plus oxytocin RR 0.73 95% CI (0.60 to 0.90), (Figure 5). Ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin were also found to be more effective when compared with misoprostol and ergometrine when used alone. There was evidence of global inconsistency in this analysis, where the direct and network (combining direct and indirect) randomised evidence were not in agreement (P = 0.046). The inconsistency was driven by a single unblinded study of ergometrine versus no treatment (Begley 1990).

Figure 5. Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for prevention of PPH ≥ 500 mL.

Ergometrine vs Placebo or control (nma)	0.66 (0.49, 0.89)
(pairwise)	0.23 (0.13, 0.42)
Misoprostol vs Placebo or control (nma)	0.61 (0.50, 0.74)
(pairwise)	0.74 (0.59, 0.93)
Misoprostol plus Oxytocin vs Placebo or control (nma)	0.41 (0.31, 0.55)
(pairwise)	na
Carbetocin vs Placebo or control (nma)	0.41 (0.28, 0.59)
(pairwise)	0.75 (0.30, 1.84)
Ergometrine plus Oxytocin vs Placebo or control (nma)	0.39 (0.30, 0.49)
(pairwise)	0.36 (0.29, 0.45)
Oxytocin vs Placebo or control (nma)	0.56 (0.46, 0.68)
(pairwise)	0.56 (0.49, 0.65)
Ergometrine vs Oxytocin (nma)	1.17 (0.90, 1.52)
(pairwise)	1.31 (0.88, 1.92)
Misoprostol vs Oxytocin (nma)	1.08 (0.95, 1.23)
(pairwise)	1.07 (0.92, 1.24)
Misoprostol plus Oxytocin vs Oxytocin (nma)	0.73 (0.60, 0.90)
(pairwise)	0.74 (0.62, 0.88)
Carbetocin vs Oxytocin (nma)	0.72 (0.52, 1.00)
(pairwise)	0.69 (0.45, 1.07)
Ergometrine plus Oxytocin vs Oxytocin (nma)	0.69 (0.57, 0.83)
(pairwise)	0.72 (0.56, 0.92)
Ergometrine vs Ergometrine plus Oxytocin (nma)	1.69 (1.24, 2.29)
(pairwise)	0.16 (0.00, 4.05)
Misoprostol vs Ergometrine plus Oxytocin (nma)	1.56 (1.29, 1.89)
(pairwise)	1.74 (1.34, 2.26)
Misoprostol plus Oxytocin vs Ergometrine plus Oxytocin (nma)	1.06 (0.81, 1.39)
(pairwise)	1.39 (0.64, 2.99)
Carbetocin vs Ergometrine plus Oxytocin (nma)	1.04 (0.73, 1.49)
(pairwise)	0.95 (0.43, 2.08)
Ergometrine vs Carbetocin (nma)	1.61 (1.06, 2.45)
(pairwise)	na
Misoprostol vs Carbetocin (nma)	1.49 (1.05, 2.11)
(pairwise)	na
Misoprostol plus Oxytocin vs Carbetocin (nma)	1.01 (0.69, 1.49)
(pairwise)	na
Ergometrine vs Misoprostol plus Oxytocin (nma)	1.58 (1.14, 2.21)
(pairwise)	na
Misoprostol vs Misoprostol plus Oxytocin (nma)	1.47 (1.16, 1.86)
(pairwise)	1.92 (0.98, 3.76)
Ergometrine vs Misoprostol (nma)	1.07 (0.83, 1.39)
(pairwise)	1.27 (0.81, 2.00)

Relative Risk (RR)

The cumulative probabilities for each agent being at each possible rank for preventing PPH ≥ 500 mL are shown in Figure 6. Ranking indicates the cumulative probability of being the best drug, the second best, the third best, etc. The highest ranked agents were ergometrine plus oxytocin combination, carbetocin, and misoprostol plus oxytocin combination with an almost 100% probability of these three agents being ranked first, second or third best. Oxytocin was ranked fourth and its probability of being ranked in the top three agents was close to 0%.

Figure 6. Cumulative rankograms comparing each of the uterotonic drugs for prevention of PPH ≥ 500 mL. Ranking indicates the cumulative probability of being the best drug, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking. We estimate the SUrface underneath this Cumulative RAnking line (SUCRA); the larger the SUCRA the higher its rank among all available drug options.
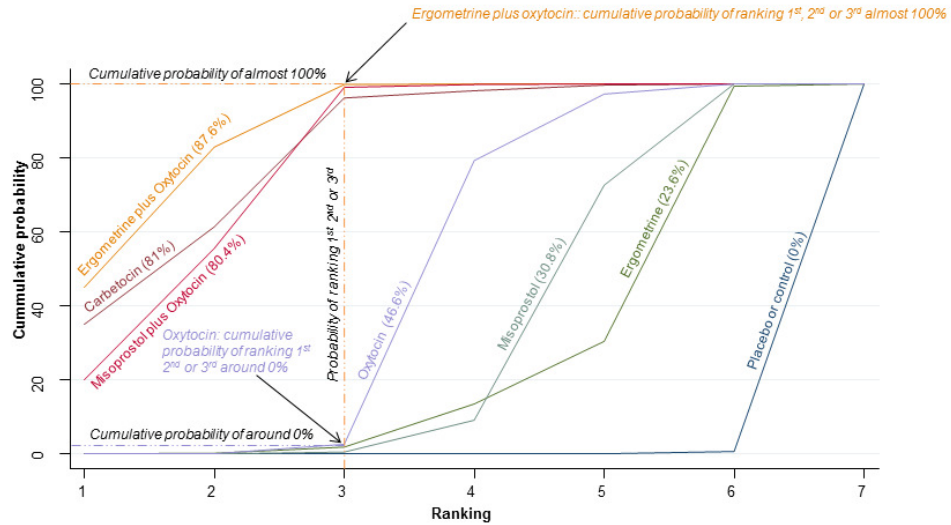
According to GRADE, the quality of evidence was rated as moderate due to inconsistency for the comparisons of ergometrine plus oxytocin versus oxytocin and misoprostol plus oxytocin versus oxytocin (Summary of findings for the main comparison). However, the quality of evidence was ranked very low for the comparison of carbetocin versus oxytocin due to the risk of bias in the studies comparing the two uterotonics, inconsistency and imprecision (Summary of findings for the main comparison).

Postpartum haemorrhage (PPH) ≥ 1000 mL

The network diagram for PPH ≥ 1000 mL is presented in Figure 7. Oxytocin was the most frequently investigated uterotonic agent (85.6%, 77 of 90 trials) (Figure 7).

Figure 7. Network diagram for PPH ≥ 1000 mL.
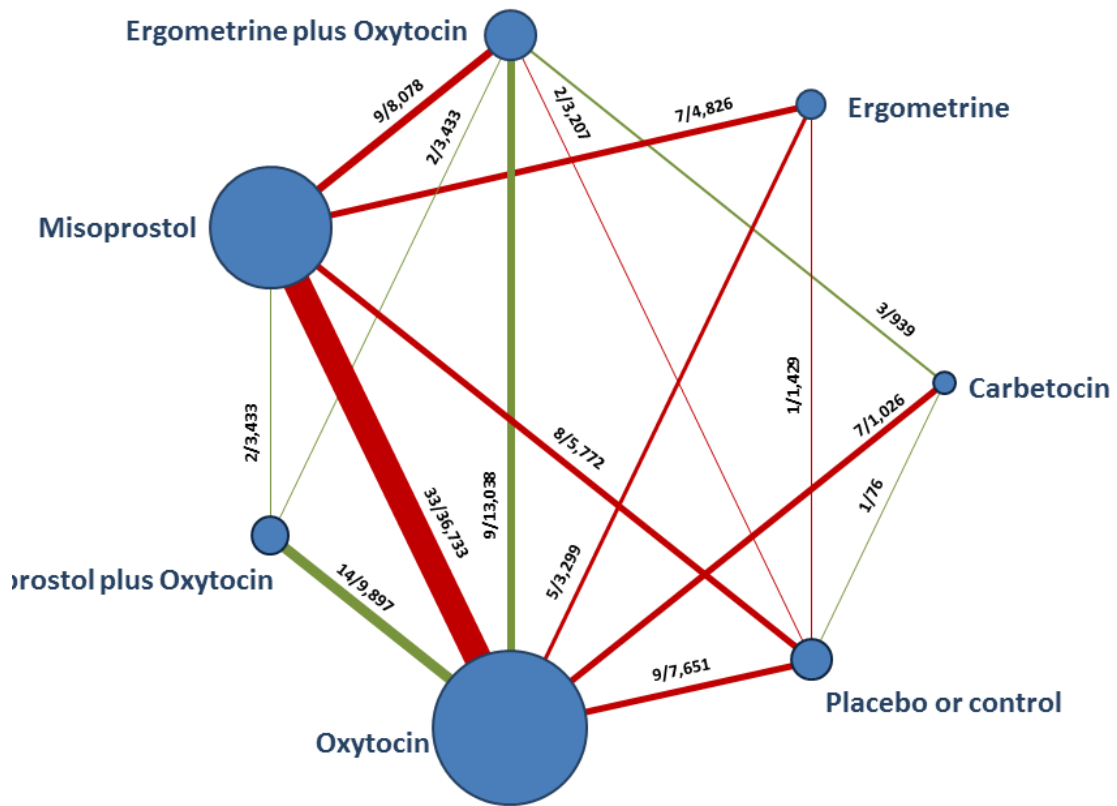
Pooled effect estimates from the network meta-analysis of 90 trials suggested that all agents except ergometrine were effective for preventing PPH ≥ 1000 mL when compared with placebo or no treatment (Figure 8). Ergometrine plus oxytocin combination was the only agent found to be more effective when compared with the standard agent oxytocin (RR 0.77, 95% CI 0.61 to 0.95) although carbetocin (RR 0.70, 95% CI 0.38 to 1.28) and misoprostol plus oxytocin combination (RR 0.90, 95% CI 0.72 to 1.14) demonstrated a trend towards reduction in this outcome (Figure 8). There was no evidence of global inconsistency (P = 0.345).

Figure 8. Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for prevention of PPH ≥ 1000 mL.

Ergometrine vs Placebo or control (nma)	0.68 (0.34, 1.35)
(pairwise)	0.09 (0.01, 0.72)
Misoprostol vs Placebo or control (nma)	0.73 (0.61, 0.88)
(pairwise)	0.73 (0.56, 0.94)
Misoprostol plus Oxytocin vs Placebo or control (nma)	0.55 (0.41, 0.73)
(pairwise)	na
Carbetocin vs Placebo or control (nma)	0.42 (0.22, 0.79)
(pairwise)	1 (0.02, 48.52)
Ergometrine plus Oxytocin vs Placebo or control (nma)	0.46 (0.36, 0.59)
(pairwise)	0.43 (0.18, 1.05)
Oxytocin vs Placebo or control (nma)	0.60 (0.51, 0.72)
(pairwise)	0.64 (0.52, 0.78)
Ergometrine vs Oxytocin (nma)	1.12 (0.57, 2.20)
(pairwise)	1.26 (0.52, 3.03)
Misoprostol vs Oxytocin (nma)	1.21 (1.01, 1.44)
(pairwise)	1.26 (1.11, 1.43)
Misoprostol plus Oxytocin vs Oxytocin (nma)	0.90 (0.72, 1.14)
(pairwise)	0.89 (0.71, 1.12)
Carbetocin vs Oxytocin (nma)	0.70 (0.38, 1.28)
(pairwise)	0.71 (0.38, 1.35)
Ergometrine plus Oxytocin vs Oxytocin (nma)	0.77 (0.61, 0.95)
(pairwise)	0.73 (0.57, 0.93)
Ergometrine vs Ergometrine plus Oxytocin (nma)	1.45 (0.72, 2.94)
(pairwise)	na
Misoprostol vs Ergometrine plus Oxytocin (nma)	1.57 (1.24, 1.99)
(pairwise)	1.59 (1.07, 2.37)
Misoprostol plus Oxytocin vs Ergometrine plus Oxytocin (nma)	1.17 (0.86, 1.60)
(pairwise)	1.40 (0.67, 2.93)
Carbetocin vs Ergometrine plus Oxytocin (nma)	0.91 (0.48, 1.71)
(pairwise)	0.69 (0.10, 4.37)
Ergometrine vs Carbetocin (nma)	1.59 (0.64, 3.93)
(pairwise)	na
Misoprostol vs Carbetocin (nma)	1.72 (0.92, 3.20)
(pairwise)	na
Misoprostol plus Oxytocin vs Carbetocin (nma)	1.29 (0.68, 2.45)
(pairwise)	na
Ergometrine vs Misoprostol plus Oxytocin (nma)	1.23 (0.60, 2.51)
(pairwise)	na
Misoprostol vs Misoprostol plus Oxytocin (nma)	1.33 (1.01, 1.75)
(pairwise)	1.85 (1.03, 3.32)
Ergometrine vs Misoprostol (nma)	0.92 (0.47, 1.82)
(pairwise)	1.68 (0.61, 4.62)

Relative Risk (RR)

The cumulative probabilities for each agent being at each possible rank for PPH ≥ 1000 mL are shown in Figure 9. The highest ranked agents were ergometrine plus oxytocin combination, carbetocin, and misoprostol plus oxytocin combination. Oxytocin was still ranked fourth and its probability of being ranked in the top three agents was approximately 20%.

Figure 9. Cumulative rankograms comparing each of the uterotonic drugs for prevention of PPH ≥ 1000 mL.
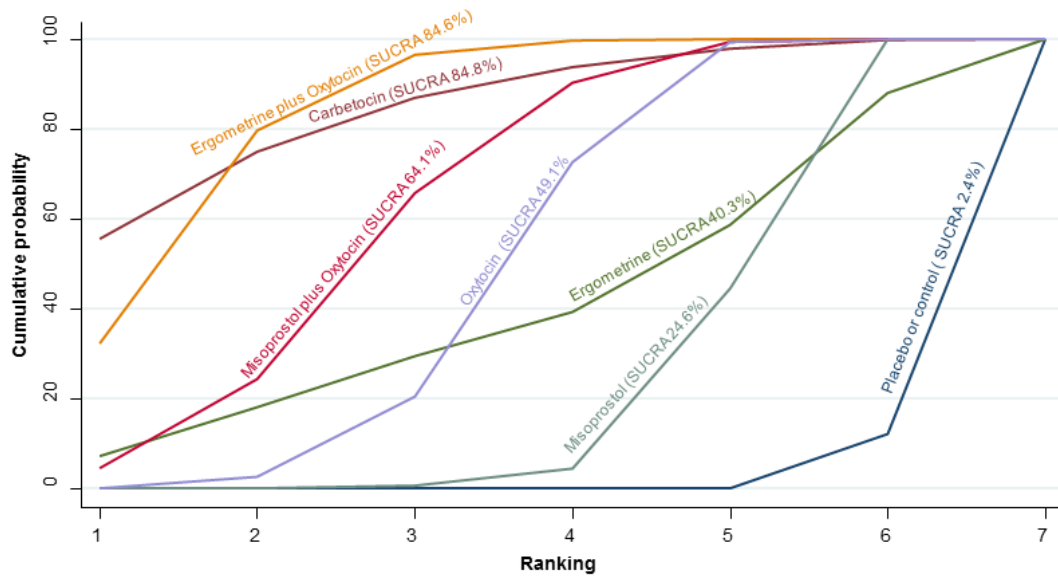
According to GRADE, the quality of evidence was rated as high for the comparison of ergometrine plus oxytocin combination versus oxytocin (Summary of findings for the main comparison). However, the quality of evidence was ranked moderate for the comparison of misoprostol plus oxytocin combination versus oxytocin due to imprecision in the confidence intervals. The quality of evidence for carbetocin versus oxytocin was ranked as low due to the risk of bias in the studies comparing the two uterotonics and the imprecision (Summary of findings for the main comparison).

Secondary outcomes

Maternal death

The network diagram for maternal death is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 50 trials suggested that there were no meaningful differences between all uterotonic agents for maternal deaths as this outcome was so rare (Figure 10). There was no evidence of global inconsistency in this analysis (P = 0.999). Figure 11 shows the cumulative probabilities for each agent being at each possible rank for maternal death. No reliable ranking could be derived for this outcome.

	RR (95% CI)
Ergometrine vs Placebo or control (nma)	1.51 (0.14, 15.87)
(pairwise)	na
Misoprostol vs Placebo or control (nma)	0.98 (0.23, 4.12)
(pairwise)	1.02 (0.14, 7.24)
Misoprostol plus Oxytocin vs Placebo or control (nma)	1.08 (0.16, 7.24)
(pairwise)	na
Carbetocin vs Placebo or control (nma)	1.05 (0.11, 9.43)
(pairwise)	na
Ergometrine plus Oxytocin vs Placebo or control (nma)	1.01 (0.13, 7.54)
(pairwise)	na
Oxytocin vs Placebo or control (nma)	1.09 (0.25, 4.58)
(pairwise)	1.04 (0.14, 7.42)
Ergometrine vs Oxytocin (nma)	1.38 (0.18, 10.12)
(pairwise)	0.91 (0.01, 45.93)
Misoprostol vs Oxytocin (nma)	0.89 (0.41, 1.92)
(pairwise)	0.89 (0.39, 2.04)
Misoprostol plus Oxytocin vs Oxytocin (nma)	0.99 (0.28, 3.46)
(pairwise)	0.99 (0.27, 3.66)
Carbetocin vs Oxytocin (nma)	0.96 (0.17, 5.25)
(pairwise)	0.99 (0.10, 9.43)
Ergometrine plus Oxytocin vs Oxytocin (nma)	0.92 (0.19, 4.31)
(pairwise)	0.99 (0.01, 50.19)
Ergometrine vs Ergometrine plus Oxytocin (nma)	1.49 (0.13, 16.04)
(pairwise)	na
Misoprostol vs Ergometrine plus Oxytocin (nma)	0.96 (0.22, 4.19)
(pairwise)	0.99 (0.17, 5.74)
Misoprostol plus Oxytocin vs Ergometrine plus Oxytocin (nma)	1.06 (0.15, 7.43)
(pairwise)	na
Carbetocin vs Ergometrine plus Oxytocin (nma)	1.04 (0.15, 6.99)
(pairwise)	1 (0.06, 15.84)
Ergometrine vs Carbetocin (nma)	1.42 (0.10, 18.59)
(pairwise)	na
Misoprostol vs Carbetocin (nma)	0.92 (0.15, 5.50)
(pairwise)	na
Misoprostol plus Oxytocin vs Carbetocin (nma)	1.02 (0.14, 7.27)
(pairwise)	1 (0.01, 50.14)
Ergometrine vs Misoprostol plus Oxytocin (nma)	1.39 (0.13, 14.53)
(pairwise)	na
Misoprostol vs Misoprostol plus Oxytocin (nma)	0.90 (0.21, 3.87)
(pairwise)	na
Ergometrine vs Misoprostol (nma)	1.53 (0.23, 10.14)
(pairwise)	1.60 (0.22, 11.35)

Relative Risk (RR)

Maternal deaths or severe morbidity

The network diagram for maternal death or severe morbidity is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 37 trials suggested that there were no detectable differences between all agents for maternal deaths or severe morbidity as this outcome was still so rare (Figure 12). There was no evidence of global inconsistency in this analysis (P = 0.884). Figure 13 shows the cumulative probabilities for each agent being at each possible rank for maternal death or severe morbidity. No sensible ranking could be derived for this outcome due to limited data.

Figure 12.   Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for maternal death or severe morbidity.
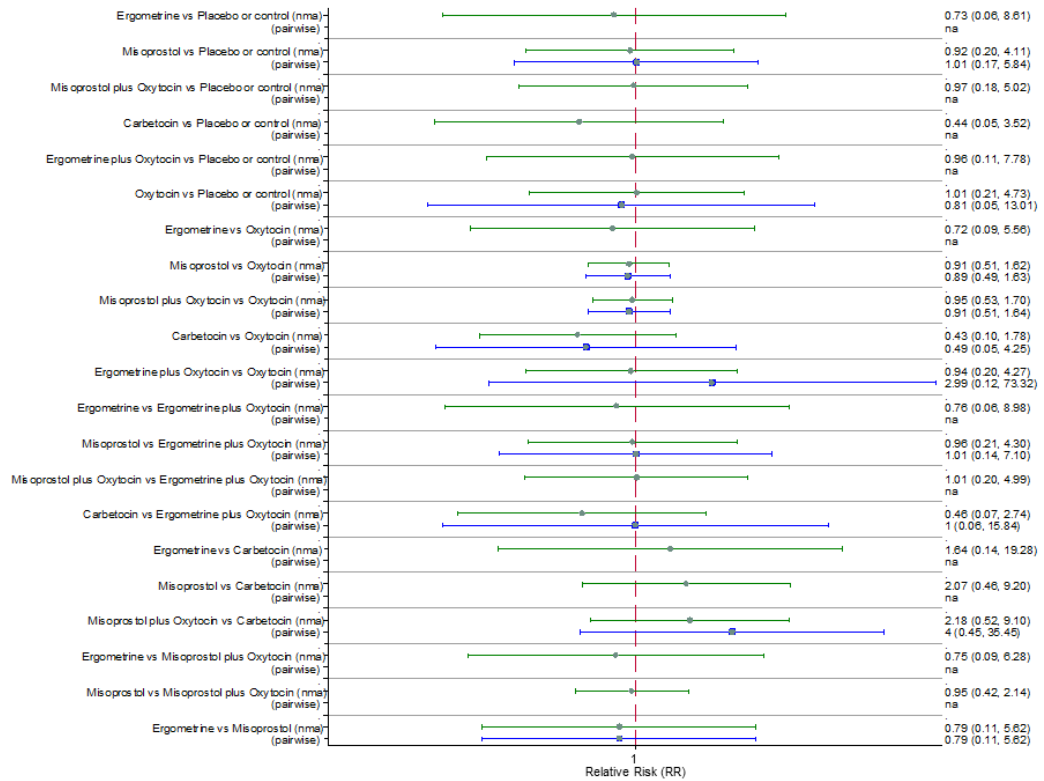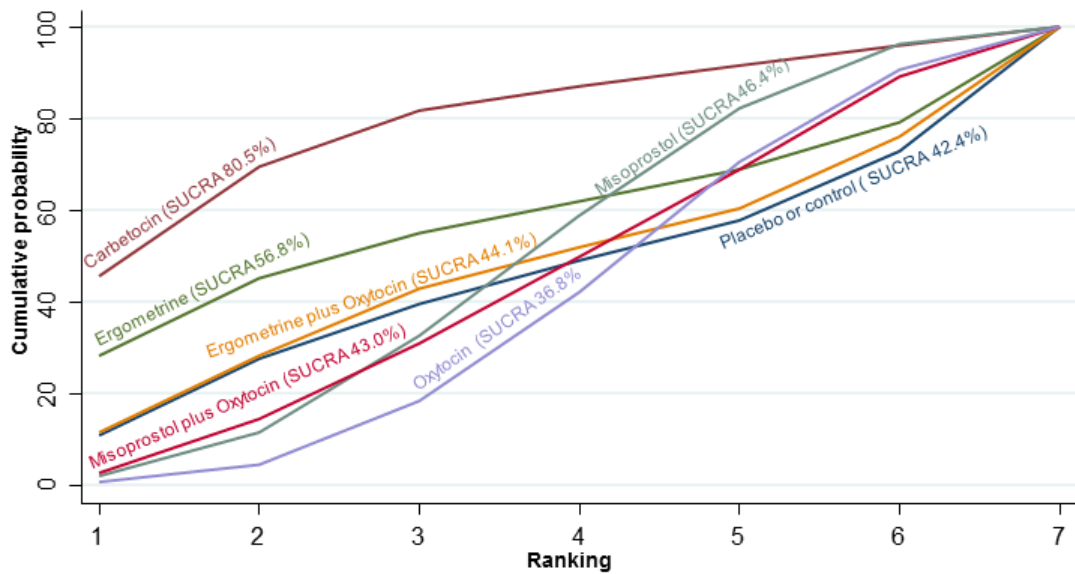
Additional uterotonics

The network diagram for the requirement of additional uterotonics is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 107 trials suggested that all agents were effective at reducing the requirement of additional uterotonics when compared with placebo or no treatment (Figure 14). Ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin were found to be more effective when compared with the standard agent oxytocin (Figure 14). Ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin were also found to be more effective when compared with misoprostol and ergometrine when used alone. There was no evidence of global inconsistency in this analysis (P = 0.275). Figure 15 shows the cumulative probabilities for each agent being at each possible rank for the requirement of additional uterotonics. The highest ranked agents were carbetocin, misoprostol plus oxytocin and ergometrine plus oxytocin with an almost 100% probability of these three agents being ranked in the top three. Oxytocin was ranked fourth and its probability in being ranked in the top three agents was close to 0%. The lowest ranked agents were misoprostol, ergometrine and placebo or no treatment.

Figure 14. Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for the requirement of additional uterotonics.
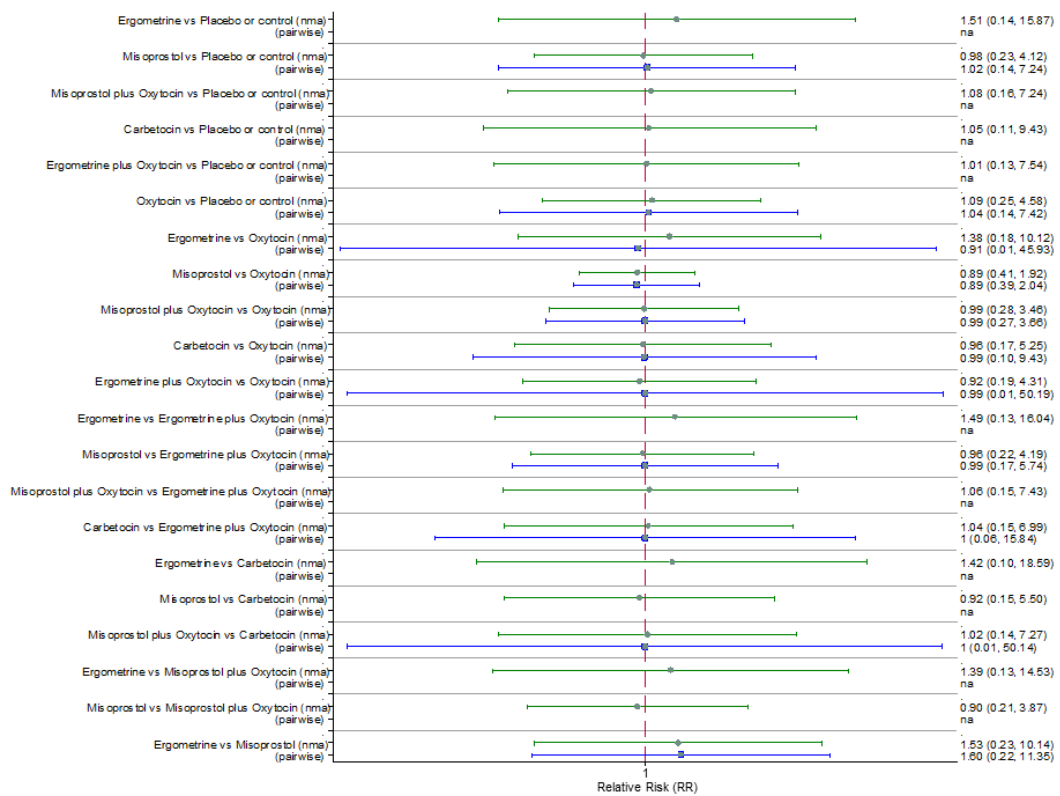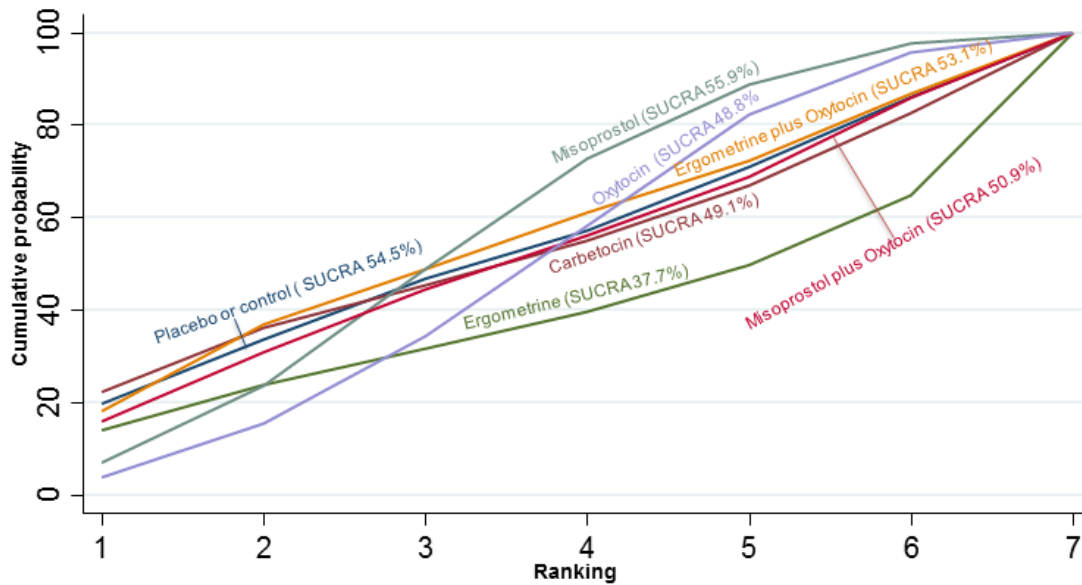

	RR (95% CI)
Ergometrine vs Placebo or control (nma)	0.44 (0.28, 0.68)
(pairwise)	0.15 (0.08, 0.26)
Misoprostol vs Placebo or control (nma)	0.43 (0.31, 0.59)
(pairwise)	0.68 (0.52, 0.88)
Misoprostol plus Oxytocin vs Placebo or control (nma)	0.23 (0.15, 0.35)
(pairwise)	na
Carbetocin vs Placebo or control (nma)	0.21 (0.13, 0.31)
(pairwise)	0.19 (0.11, 0.32)
Ergometrine plus Oxytocin vs Placebo or control (nma)	0.25 (0.18, 0.37)
(pairwise)	0.19 (0.15, 0.24)
Oxytocin vs Placebo or control (nma)	0.40 (0.29, 0.55)
(pairwise)	0.43 (0.28, 0.65)
Ergometrine vs Oxytocin (nma)	1.08 (0.75, 1.55)
(pairwise)	1.45 (0.60, 3.48)
Misoprostol vs Oxytocin (nma)	1.07 (0.89, 1.29)
(pairwise)	1.02 (0.85, 1.24)
Misoprostol plus Oxytocin vs Oxytocin (nma)	0.57 (0.42, 0.77)
(pairwise)	0.55 (0.44, 0.69)
Carbetocin vs Oxytocin (nma)	0.51 (0.37, 0.71)
(pairwise)	0.56 (0.32, 0.95)
Ergometrine plus Oxytocin vs Oxytocin (nma)	0.63 (0.48, 0.84)
(pairwise)	0.75 (0.55, 1.04)
Ergometrine vs Ergometrine plus Oxytocin (nma)	1.69 (1.10, 2.61)
(pairwise)	na
Misoprostol vs Ergometrine plus Oxytocin (nma)	1.68 (1.26, 2.24)
(pairwise)	1.87 (1.48, 2.36)
Misoprostol plus Oxytocin vs Ergometrine plus Oxytocin (nma)	0.89 (0.60, 1.32)
(pairwise)	1.48 (0.82, 2.68)
Carbetocin vs Ergometrine plus Oxytocin (nma)	0.81 (0.56, 1.16)
(pairwise)	0.72 (0.43, 1.20)
Ergometrine vs Carbetocin (nma)	2.09 (1.30, 3.36)
(pairwise)	na
Misoprostol vs Carbetocin (nma)	2.07 (1.45, 2.96)
(pairwise)	na
Misoprostol plus Oxytocin vs Carbetocin (nma)	1.10 (0.73, 1.67)
(pairwise)	1.19 (0.73, 1.92)
Ergometrine vs Misoprostol plus Oxytocin (nma)	1.89 (1.18, 3.00)
(pairwise)	na
Misoprostol vs Misoprostol plus Oxytocin (nma)	1.87 (1.33, 2.63)
(pairwise)	2.11 (1.35, 3.31)
Ergometrine vs Misoprostol (nma)	1.00 (0.71, 1.42)
(pairwise)	1.13 (0.70, 1.82)

Relative Risk (RR)

Figure 15. Cumulative rankograms comparing each of the uterotonic drugs for the requirement of additional uterotonics.
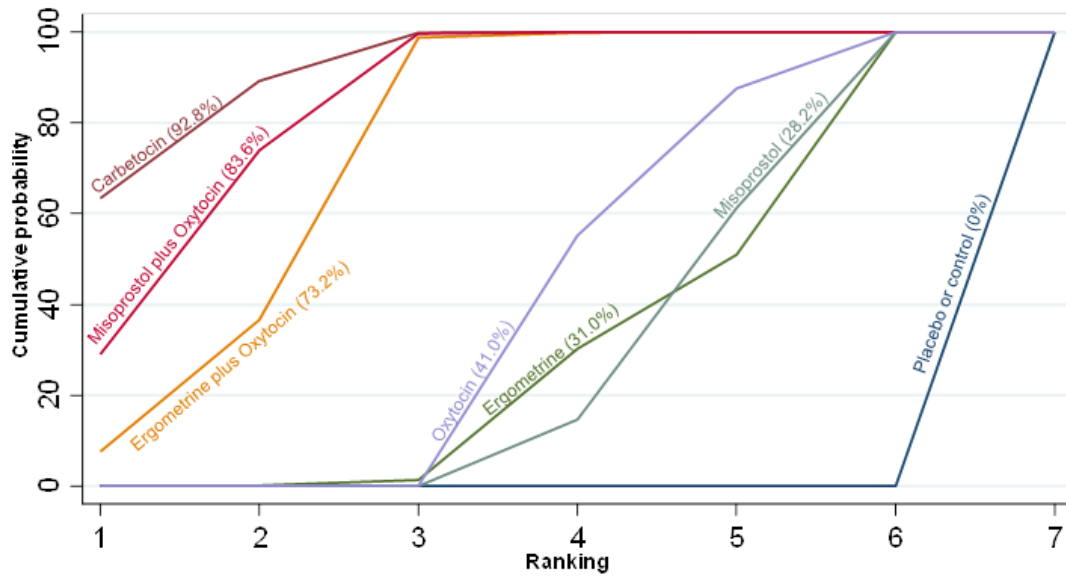
Transfusion

The network diagram for blood transfusion is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 92 trials suggested that all agents except ergometrine were effective for preventing blood transfusion when compared with placebo or no treatment (Figure 16). Misoprostol plus oxytocin was the only agent found to be more effective when compared with the standard agent oxytocin. Carbetocin and ergometrine plus oxytocin demonstrated a trend towards reduction of this outcome (Figure 16). There was no evidence of global inconsistency in this analysis (P = 0.061). Figure 17 shows the cumulative probabilities for each agent being at each possible rank for preventing blood transfusion. The highest ranked agents were misoprostol plus oxytocin, carbetocin and ergometrine plus oxytocin. Oxytocin was ranked fifth behind misoprostol and its probability of being ranked in the top three agents was less than 10%.

**Figure 16. Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for the requirement of blood transfusion.**
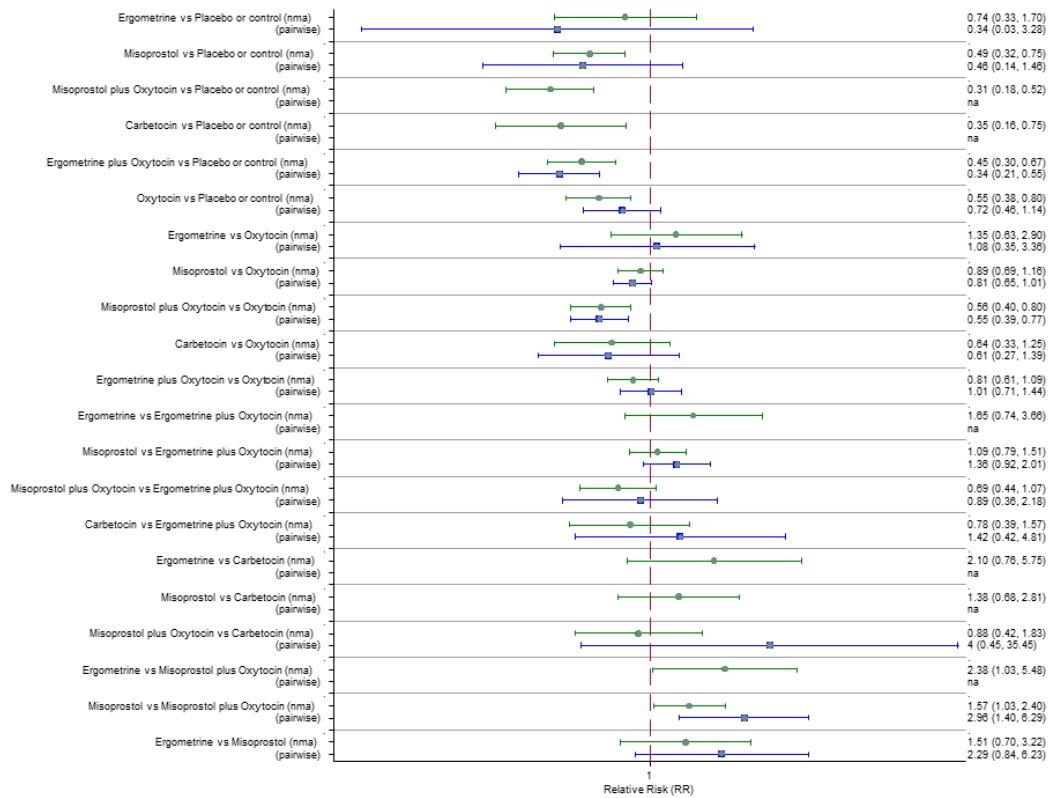
Figure 17. Cumulative rankograms comparing each of the uterotonic drugs for the requirement of blood transfusion.
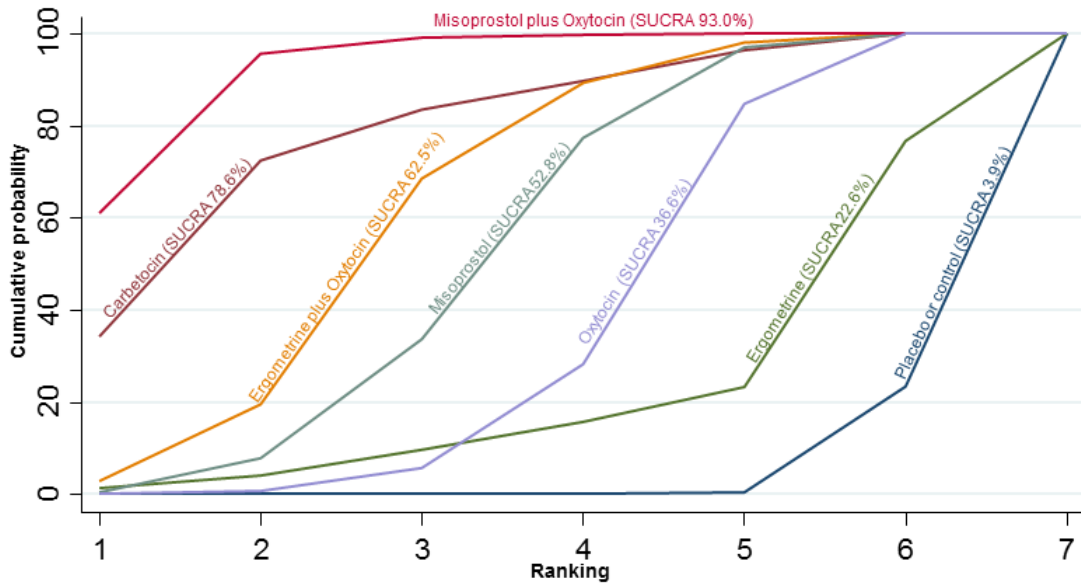
Manual removal of the placenta

The network diagram for the requirement of manual removal of placenta is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 67 trials suggested that there are no clear differences between all agents for this outcome (Figure 18). There was evidence of global inconsistency in this analysis (P = 0.025). However, we note that the CIs for both the network meta-analysis and direct evidence were overlapping across all compar-

isons suggesting locally-consistent results except for ergometrine versus placebo or no treatment and carbetocin versus oxytocin based on single studies. Figure 19 shows the cumulative probabilities for each agent being at each possible rank for prevention of the manual removal of placenta. No clear ranking could be derived for this outcome with all agents being comparable, except for carbetocin that appeared to have the highest probability in being the top ranked agent with a probability close to 80%.

Figure 18.   Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for the requirement of manual removal of placenta.
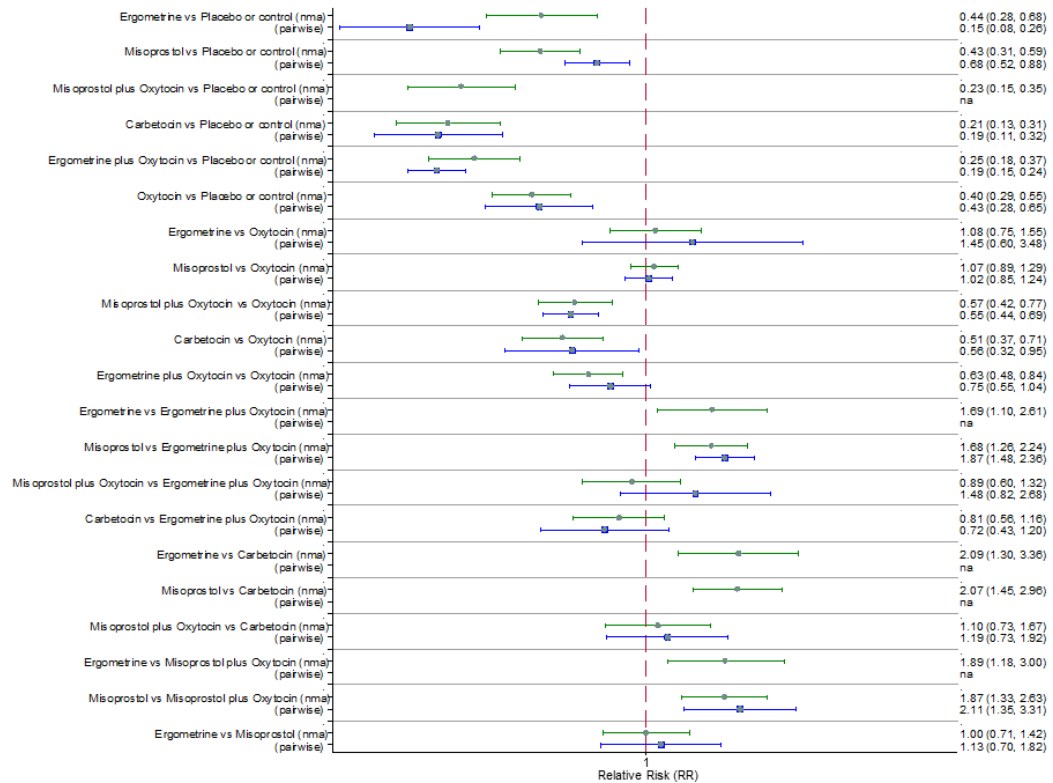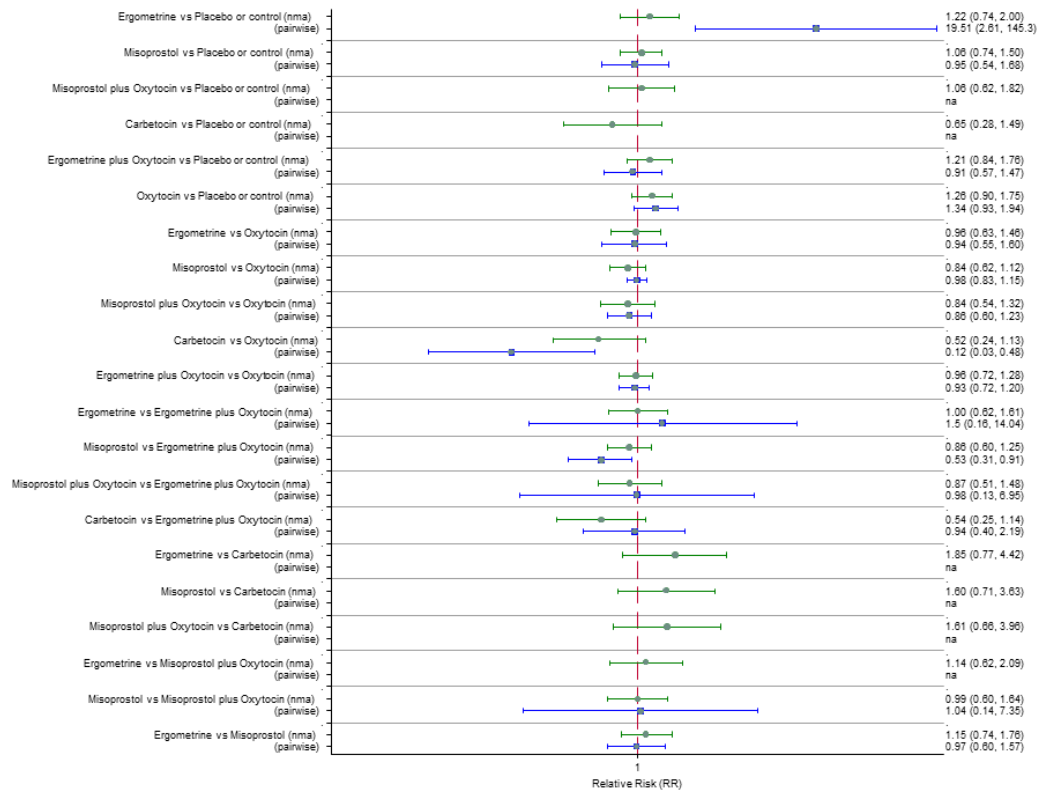
Figure 19. Cumulative rankograms comparing each of the uterotonic drugs for the requirement of manual removal of placenta.
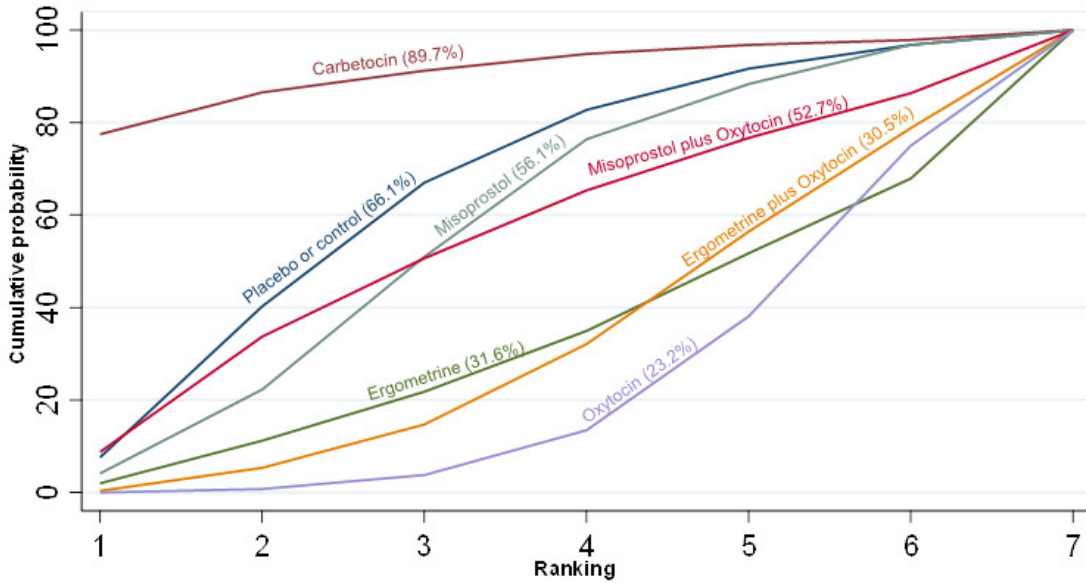
Mean volumes of blood loss

The network diagram for blood loss (mL) as a continuous outcome is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 102 trials suggested that all agents are effective for reducing blood loss as a continuous outcome when compared with placebo or no treatment (Figure 20). Carbetocin and misoprostol plus oxytocin were found to be more effective when compared with the standard agent oxytocin. Ergometrine plus oxytocin also demonstrated a trend towards reduction of this outcome (Figure 20). Carbetocin and misoprostol plus oxytocin were more effective than ergometrine plus oxytocin in reducing blood loss. Carbetocin and misoprostol plus oxytocin were also found to be more effective when compared with misoprostol and ergometrine when used alone. There was no evidence of global inconsistency in this analysis (P = 0.111). Figure 21 shows the cumulative probabilities for each agent being at each possible rank for preventing blood loss (mL) as a continuous outcome. The highest ranked agents were carbetocin, misoprostol plus oxytocin and ergometrine plus oxytocin. Oxytocin was ranked fourth and its probability in being ranked in the top three agents was less than 10%. The lowest ranked agents were misoprostol, ergometrine and placebo or no treatment.

**Figure 20. Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for blood loss (mL).**

Ergometrine vs Placebo or control (nma)	-43.9 (-86.9, -0.98)
(pairwise)	-85.9 (-104.7089, -67.0)
Misoprostol vs Placebo or control (nma)	-57.8 (-92.5, -23.0)
(pairwise)	-34.2 (-65.8, -2.67)
Misoprostol plus Oxytocin vs Placebo or control (nma)	-124.7588 (-173.6839, -75.8)
(pairwise)	na
Carbetocin vs Placebo or control (nma)	-138.0504 (-189.6751, -86.4)
(pairwise)	-274 (-591.6054, 43.6)
Ergometrine plus Oxytocin vs Placebo or control (nma)	-79.8 (-121.09, -38.5)
(pairwise)	-35.0 (-101.633, 31.5)
Oxytocin vs Placebo or control (nma)	-58.2 (-93.3, -23.0)
(pairwise)	-105.8845 (-134.964, -76.8)
Ergometrine vs Oxytocin (nma)	14.2 (-16.8, 45.3)
(pairwise)	16.7 (-9.30, 42.7)
Misoprostol vs Oxytocin (nma)	0.41 (-18.7, 19.5)
(pairwise)	-0.34 (-15.2, 14.5)
Misoprostol plus Oxytocin vs Oxytocin (nma)	-66.5 (-101.2554, -31.8)
(pairwise)	-73.0 (-139.0105, -7.11)
Carbetocin vs Oxytocin (nma)	-79.8 (-120.0949, -39.5)
(pairwise)	-73.6 (-130.0086, -17.3)
Ergometrine plus Oxytocin vs Oxytocin (nma)	-21.6 (-51.5, 8.36)
(pairwise)	-13.1 (-54.0, 27.7)
Ergometrine vs Ergometrine plus Oxytocin (nma)	35.8 (-3.95, 75.6)
(pairwise)	20.1 (5.76, 34.4)
Misoprostol vs Ergometrine plus Oxytocin (nma)	22.0 (-8.60, 52.6)
(pairwise)	22.8 (4.50, 41.2)
Misoprostol plus Oxytocin vs Ergometrine plus Oxytocin (nma)	-44.9 (-89.2, -0.55)
(pairwise)	-16 (-40.2, 8.22)
Carbetocin vs Ergometrine plus Oxytocin (nma)	-58.2 (-100.6883, -15.7)
(pairwise)	-48.8 (-94.8, -2.84)
Ergometrine vs Carbetocin (nma)	94.0 (44.3, 143.)
(pairwise)	na
Misoprostol vs Carbetocin (nma)	80.2 (37.1, 123.)
(pairwise)	na
Misoprostol plus Oxytocin vs Carbetocin (nma)	13.2 (-37.3, 63.9)
(pairwise)	106 (52.6, 159.)
Ergometrine vs Misoprostol plus Oxytocin (nma)	80.7 (34.5, 127.)
(pairwise)	na
Misoprostol vs Misoprostol plus Oxytocin (nma)	66.9 (27.9, 105.)
(pairwise)	48 (24.6, 71.3)
Ergometrine vs Misoprostol (nma)	13.8 (-17.1, 44.8)
(pairwise)	21.7 (-7.32, 50.7)

0
Mean Difference (md)

Figure 21. Cumulative rankograms comparing each of the uterotonic drugs for blood loss (mL).
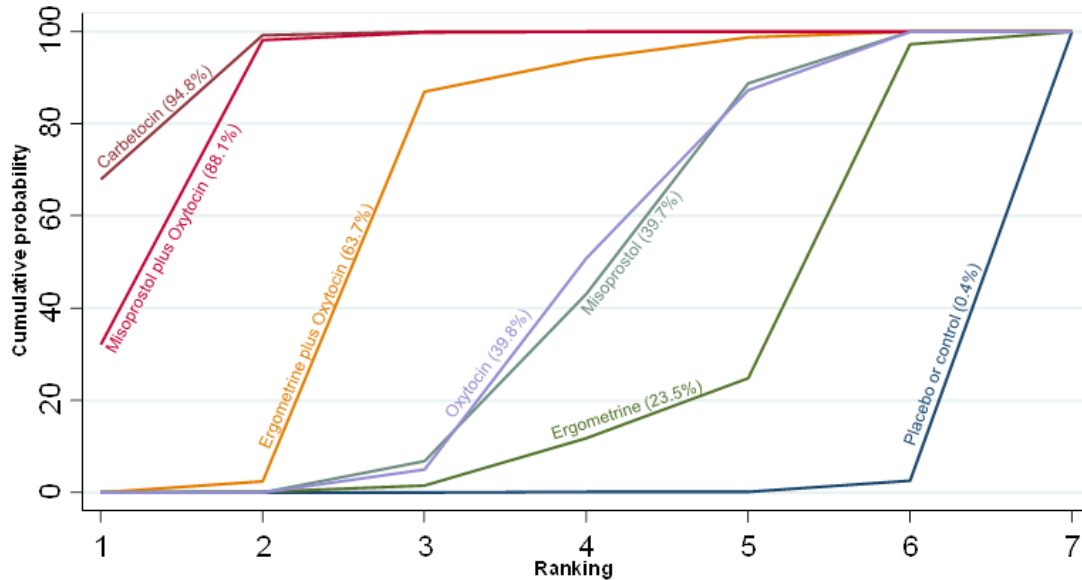
Mean durations of the third stage of labour

The network diagram for the duration of the third stage (minutes) as a continuous outcome is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 58 trials suggested that all agents are effective for reducing the duration of the third stage as a continuous outcome when compared with placebo or no treatment except for carbetocin and misoprostol plus oxytocin that demonstrated a similar trend towards reduction of this outcome (Figure 22). There were no significant differences between all active agents for this outcome (Figure 22). There was evidence of global inconsistency in this analysis (P = 0.011) and these results need to be interpreted with caution. Figure 23 shows the cumulative probabilities for each agent being at each possible rank for the reduction of the duration of the third stage. No sensible ranking could be derived for this outcome with all agents being comparable. The exception was ergometrine plus oxytocin that appeared to have the highest probability in being the top ranked agent with a probability close to 60% and the placebo or no treatment that appeared to have the lowest ranking.

Figure 22. Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for duration of third stage (minutes).
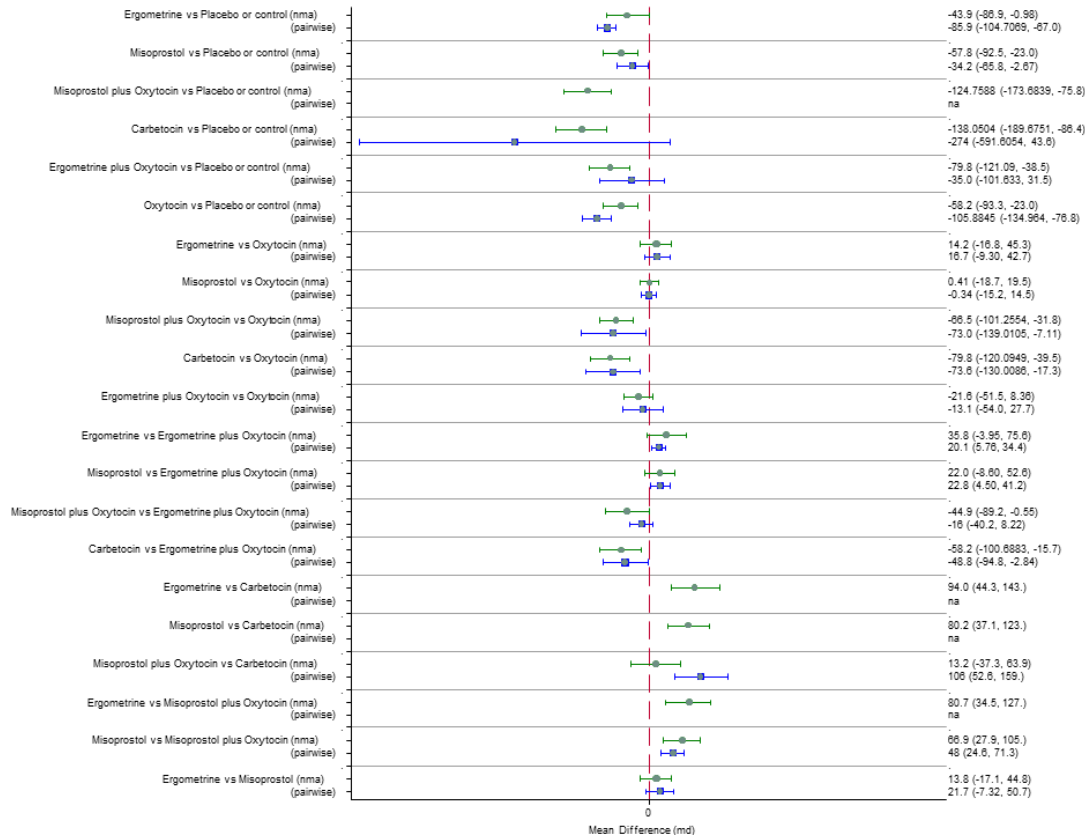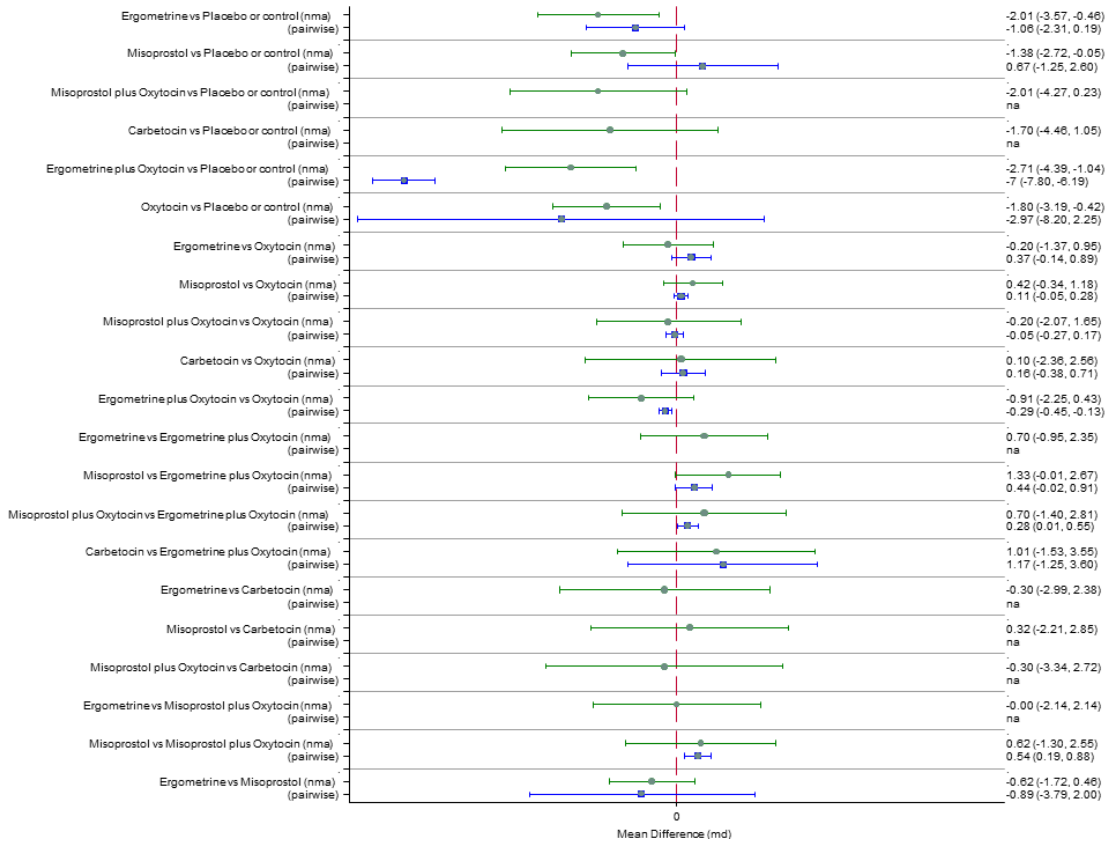

|	
Ergometrine vs Placebo or control (nma)	-2.01 (-3.57, -0.46)
(pairwise)	-1.06 (-2.31, 0.19)
Misoprostol vs Placebo or control (nma)	-1.38 (-2.72, -0.05)
(pairwise)	0.67 (-1.25, 2.60)
Misoprostol plus Oxytocin vs Placebo or control (nma)	-2.01 (-4.27, 0.23)
(pairwise)	na
Carbetocin vs Placebo or control (nma)	-1.70 (-4.46, 1.05)
(pairwise)	na
Ergometrine plus Oxytocin vs Placebo or control (nma)	-2.71 (-4.39, -1.04)
(pairwise)	-7 (-7.80, -6.19)
Oxytocin vs Placebo or control (nma)	-1.80 (-3.19, -0.42)
(pairwise)	-2.97 (-8.20, 2.25)
Ergometrine vs Oxytocin (nma)	-0.20 (-1.37, 0.95)
(pairwise)	0.37 (-0.14, 0.89)
Misoprostol vs Oxytocin (nma)	0.42 (-0.34, 1.18)
(pairwise)	0.11 (-0.05, 0.28)
Misoprostol plus Oxytocin vs Oxytocin (nma)	-0.20 (-2.07, 1.65)
(pairwise)	-0.05 (-0.27, 0.17)
Carbetocin vs Oxytocin (nma)	0.10 (-2.36, 2.56)
(pairwise)	0.16 (-0.38, 0.71)
Ergometrine plus Oxytocin vs Oxytocin (nma)	-0.91 (-2.25, 0.43)
(pairwise)	-0.29 (-0.45, -0.13)
Ergometrine vs Ergometrine plus Oxytocin (nma)	0.70 (-0.95, 2.35)
(pairwise)	na
Misoprostol vs Ergometrine plus Oxytocin (nma)	1.33 (-0.01, 2.67)
(pairwise)	0.44 (-0.02, 0.91)
Misoprostol plus Oxytocin vs Ergometrine plus Oxytocin (nma)	0.70 (-1.40, 2.81)
(pairwise)	0.28 (0.01, 0.55)
Carbetocin vs Ergometrine plus Oxytocin (nma)	1.01 (-1.53, 3.55)
(pairwise)	1.17 (-1.25, 3.60)
Ergometrine vs Carbetocin (nma)	-0.30 (-2.99, 2.38)
(pairwise)	na
Misoprostol vs Carbetocin (nma)	0.32 (-2.21, 2.85)
(pairwise)	na
Misoprostol plus Oxytocin vs Carbetocin (nma)	-0.30 (-3.34, 2.72)
(pairwise)	na
Ergometrine vs Misoprostol plus Oxytocin (nma)	-0.00 (-2.14, 2.14)
(pairwise)	na
Misoprostol vs Misoprostol plus Oxytocin (nma)	0.62 (-1.30, 2.55)
(pairwise)	0.54 (0.19, 0.88)
Ergometrine vs Misoprostol (nma)	-0.62 (-1.72, 0.46)
(pairwise)	-0.89 (-3.79, 2.00)

0
Mean Difference (md)

Figure 23. Cumulative rankograms comparing each of the uterotonic drugs for duration of third stage (minutes).
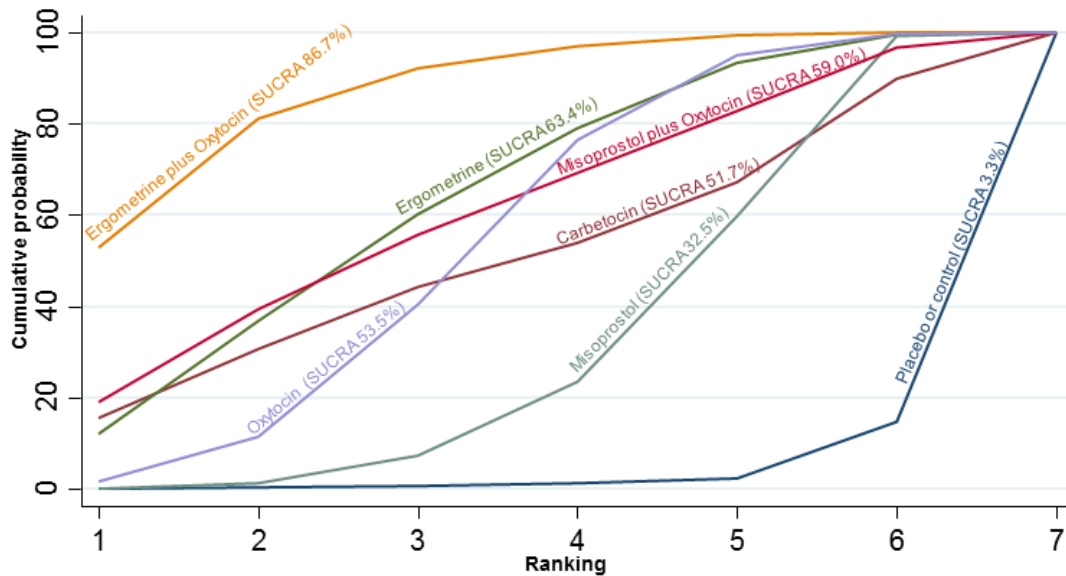
Change in haemoglobin

The network diagram for the change in haemoglobin measurements before and after birth (g/L) is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 74 trials suggested that misoprostol plus oxytocin and carbetocin are effective for reducing the change in haemoglobin measurements when compared with placebo or no treatment (Figure 24). Misoprostol plus oxytocin was the only agent found to be more effective when compared with the standard agent oxytocin (Figure 24). The combination of misoprostol plus oxytocin was also more effective than misoprostol and ergometrine when used alone. Carbetocin was more effective than ergometrine when used alone. However, there was evidence of substantial global inconsistency in this analysis (P = 0.001). Figure 25 shows the cumulative probabilities for each agent being at each possible rank for change in haemoglobin measurements before and after birth (g/L). The highest ranked agents were misoprostol plus oxytocin, carbetocin and ergometrine plus oxytocin. Oxytocin was ranked fourth and its probability in being ranked in the top three agents was just over 20%. The lowest ranked agents were misoprostol, ergometrine and placebo or no treatment.

Figure 24. Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for change in haemoglobin measurements before and after birth (g/L).
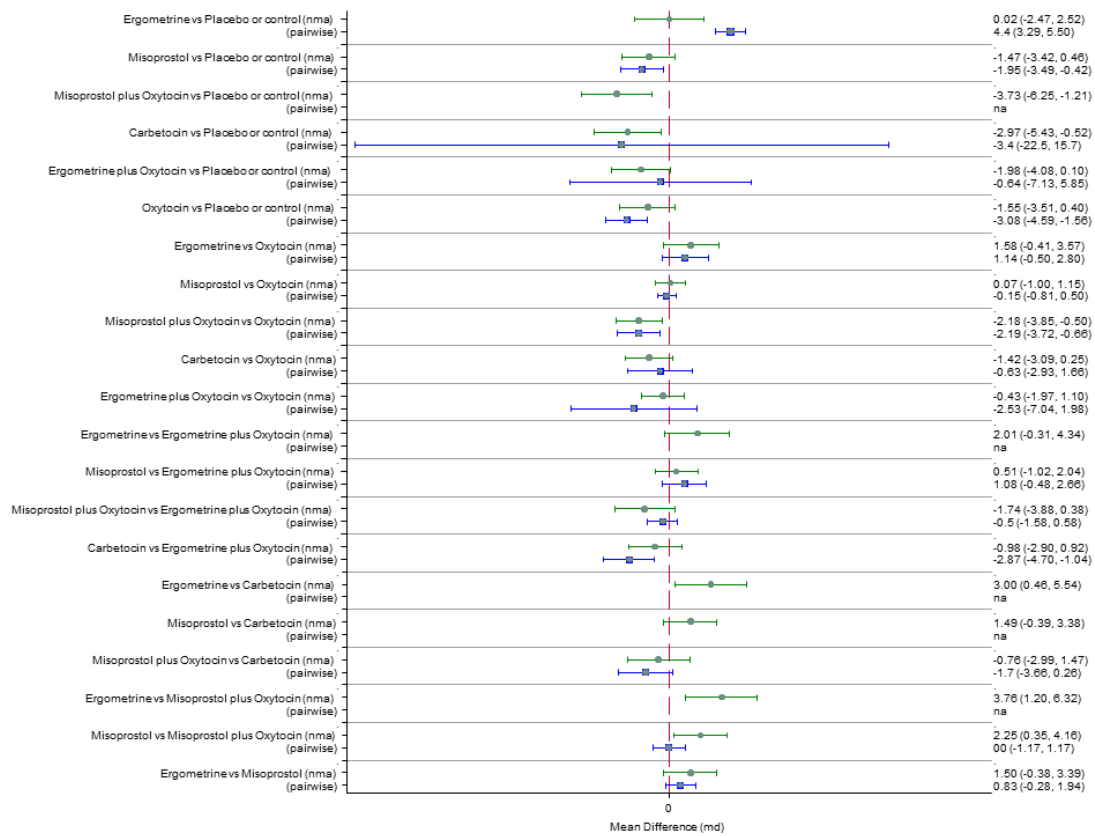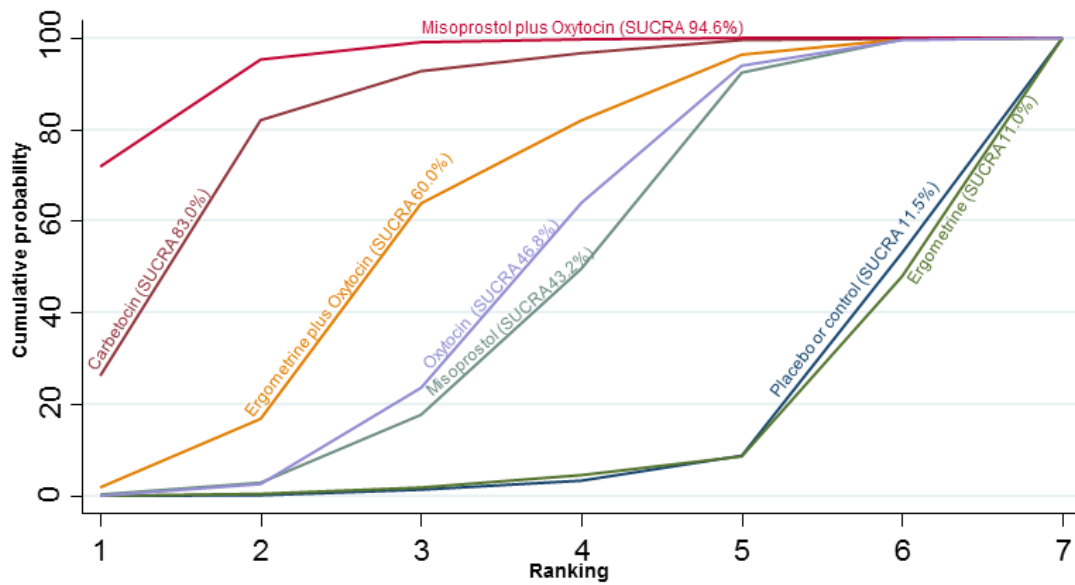
Figure 25. Cumulative rankograms comparing each of the uterotonic drugs for change in haemoglobin measurements before and after birth (g/L).

Clinical signs of blood loss

There were no trials reporting clinical signs of acute blood loss.

Neonatal unit admission

The network diagram for neonatal unit admissions is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of only six trials did not point towards any meaningful differences between all agents for this outcome (Figure 26). There was no evidence of global inconsistency in this analysis (P = 0.989). Figure 27 shows the cumulative probabilities for each agent being at each possible rank for neonatal unit admissions. No sensible ranking could be derived for this outcome because of too few studies reporting this outcome.

Figure 26. Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for neonatal unit admissions.

Figure 27. Cumulative rankograms comparing each of the uterotonic drugs for neonatal unit admissions.
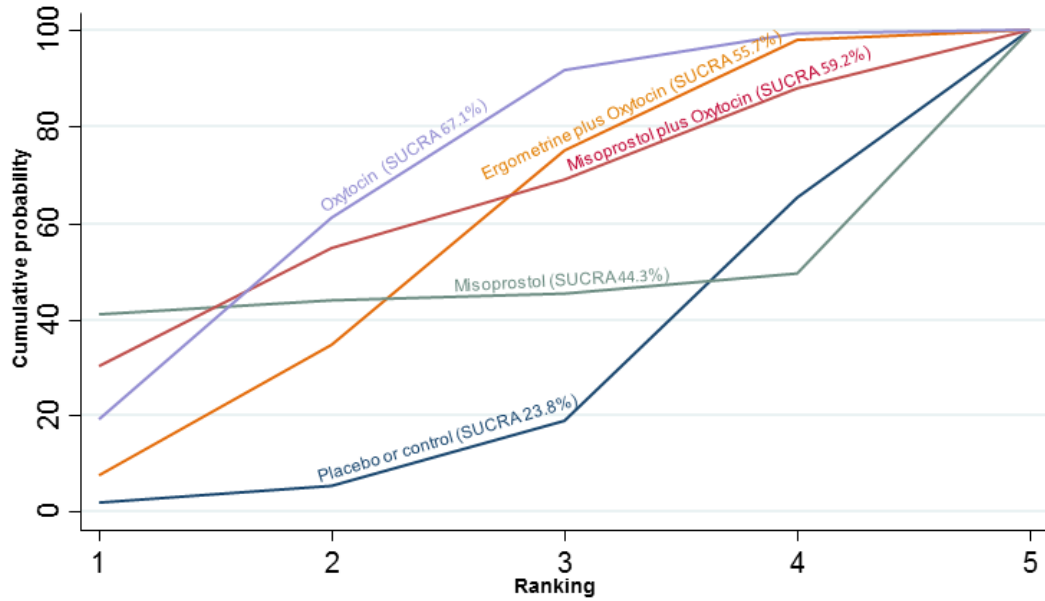
Breastfeeding at discharge

The network diagram for breastfeeding at discharge is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of only five trials did not point towards any meaningful differences between agents for this outcome (Figure 28). There was no evidence of global inconsistency in this analysis (P = 0.167). Figure 29 shows the cumulative probabilities for each agent being at each possible rank for breastfeeding at discharge. No clear ranking could be derived for this outcome with all agents being comparable again because of too few studies.

Figure 28. Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for breastfeeding at discharge.

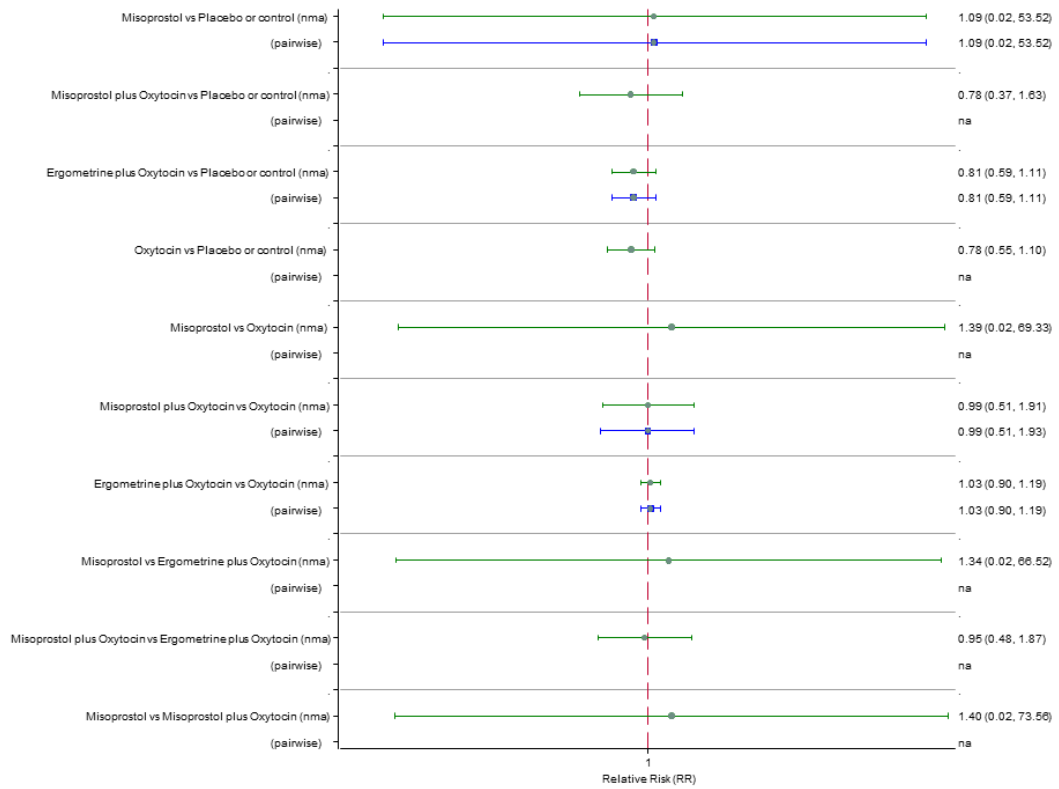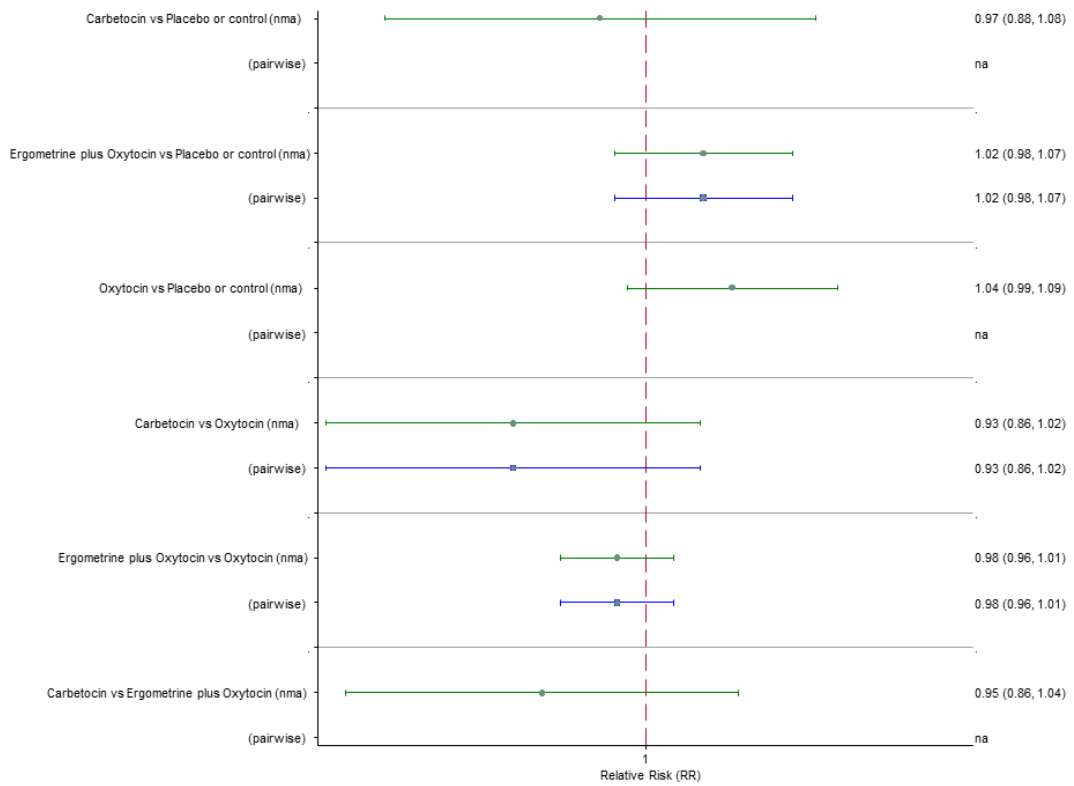**Figure 29. Cumulative rankograms comparing each of the uterotonic drugs for breastfeeding at discharge.**
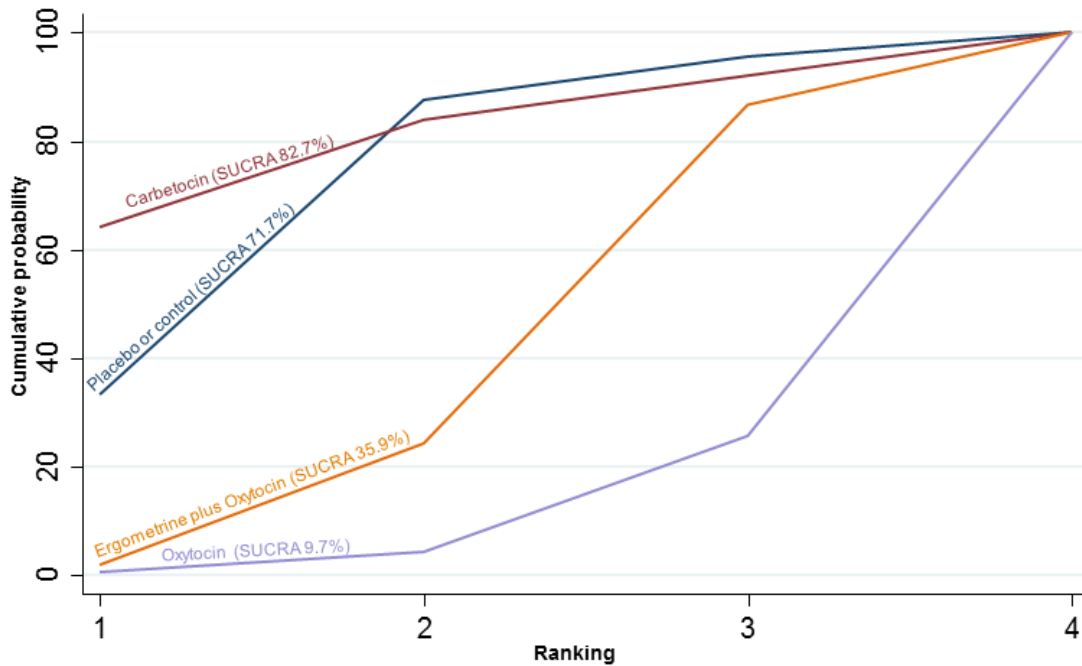
Side-effects

Nausea

The network diagram for nausea is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 74 trials suggested that ergometrine and ergometrine plus oxytocin are worse than placebo or no treatment in causing nausea (Figure 30). Ergometrine, ergometrine plus oxytocin, misoprostol and misoprostol plus oxytocin were found to be worse in causing nausea when compared with the standard agent oxytocin (Figure 30). Er-

gometrine, ergometrine plus oxytocin and misoprostol plus oxytocin were significantly worse in causing nausea than carbetocin. There was evidence of global inconsistency in this analysis (P = 0.005). However, we note that the CIs for both the network meta-analysis and direct evidence were overlapping across all comparisons suggesting locally-consistent results except for ergometrine versus placebo or no treatment based on a single study. Figure 31 shows the cumulative probabilities for each agent being at each possible rank for causing nausea. The highest ranked and the agents with the least risk of nausea were carbetocin, oxytocin and placebo or no treatment. The lowest ranked and most likely agents to cause nausea were ergometrine plus oxytocin and ergometrine.

Figure 30.   Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for nausea.

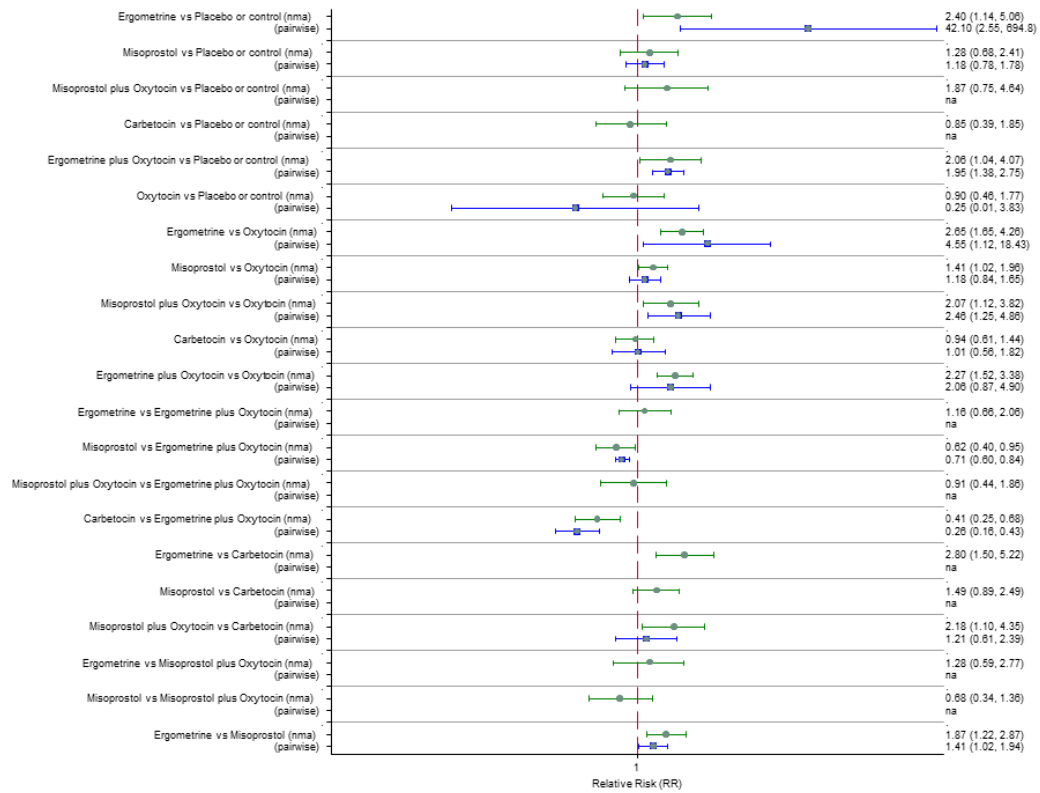|	
Ergometrine vs Placebo or control (nma) (pairwise)	2.40 (1.14, 5.06) 42.10 (2.55, 694.8)
Misoprostol vs Placebo or control (nma) (pairwise)	1.28 (0.68, 2.41) 1.18 (0.78, 1.78)
Misoprostol plus Oxytocin vs Placebo or control (nma) (pairwise)	1.87 (0.75, 4.64) na
Carbetocin vs Placebo or control (nma) (pairwise)	0.85 (0.39, 1.85) na
Ergometrine plus Oxytocin vs Placebo or control (nma) (pairwise)	2.06 (1.04, 4.07) 1.95 (1.38, 2.75)
Oxytocin vs Placebo or control (nma) (pairwise)	0.90 (0.46, 1.77) 0.25 (0.01, 3.83)
Ergometrine vs Oxytocin (nma) (pairwise)	2.65 (1.65, 4.26) 4.55 (1.12, 18.43)
Misoprostol vs Oxytocin (nma) (pairwise)	1.41 (1.02, 1.96) 1.18 (0.84, 1.65)
Misoprostol plus Oxytocin vs Oxytocin (nma) (pairwise)	2.07 (1.12, 3.82) 2.46 (1.25, 4.86)
Carbetocin vs Oxytocin (nma) (pairwise)	0.94 (0.61, 1.44) 1.01 (0.56, 1.82)
Ergometrine plus Oxytocin vs Oxytocin (nma) (pairwise)	2.27 (1.52, 3.38) 2.06 (0.87, 4.90)
Ergometrine vs Ergometrine plus Oxytocin (nma) (pairwise)	1.16 (0.66, 2.06) na
Misoprostol vs Ergometrine plus Oxytocin (nma) (pairwise)	0.62 (0.40, 0.95) 0.71 (0.60, 0.84)
Misoprostol plus Oxytocin vs Ergometrine plus Oxytocin (nma) (pairwise)	0.91 (0.44, 1.86) na
Carbetocin vs Ergometrine plus Oxytocin (nma) (pairwise)	0.41 (0.25, 0.68) 0.26 (0.16, 0.43)
Ergometrine vs Carbetocin (nma) (pairwise)	2.80 (1.50, 5.22) na
Misoprostol vs Carbetocin (nma) (pairwise)	1.49 (0.89, 2.49) na
Misoprostol plus Oxytocin vs Carbetocin (nma) (pairwise)	2.18 (1.10, 4.35) 1.21 (0.61, 2.39)
Ergometrine vs Misoprostol plus Oxytocin (nma) (pairwise)	1.28 (0.59, 2.77) na
Misoprostol vs Misoprostol plus Oxytocin (nma) (pairwise)	0.68 (0.34, 1.36) na
Ergometrine vs Misoprostol (nma) (pairwise)	1.87 (1.22, 2.87) 1.41 (1.02, 1.94)

Relative Risk (RR)

Figure 31. Cumulative rankograms comparing each of the uterotonic drugs for nausea.
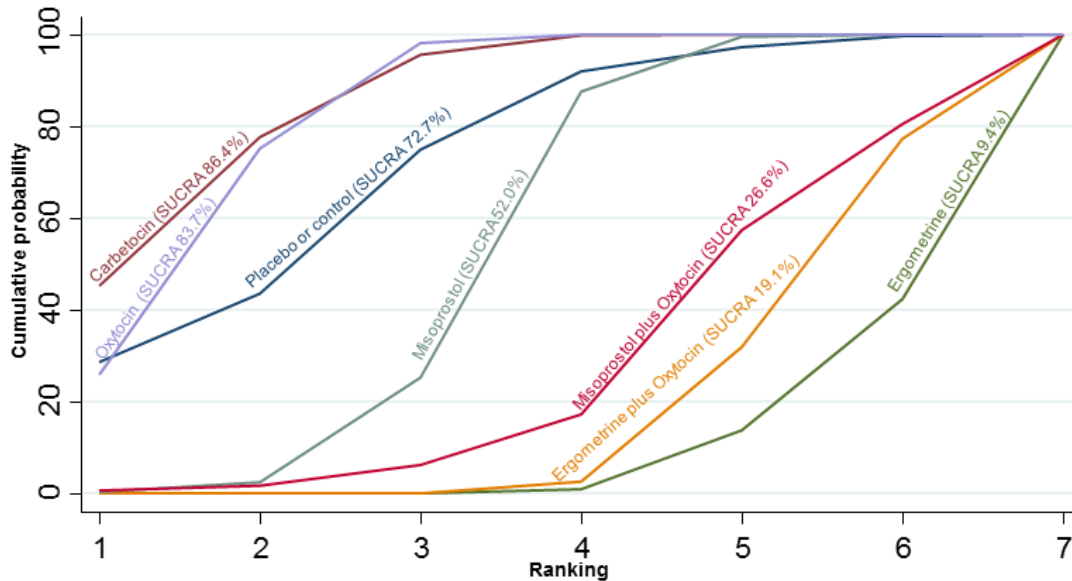
Vomiting

The network diagram for vomiting is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 83 trials suggested that ergometrine and ergometrine plus oxytocin are worse than placebo or no treatment in causing vomiting (Figure 32). Ergometrine, ergometrine plus oxytocin, misoprostol and misoprostol plus ocytocin were found to be worse in causing vomiting when compared with the standard agent oxytocin (Figure 32).

Ergometrine, ergometrine plus oxytocin, misoprostol and misoprostol plus oxytocin were significantly worse in causing vomiting than carbetocin. There was no evidence of global inconsistency in this analysis (P = 0.06). Figure 33 shows the cumulative probabilities for each agent being at each possible rank for causing vomiting. The highest ranked agents were carbetocin, oxytocin and placebo or no treatment with an almost 100% probability of these three agents being ranked in the top three. The lowest ranked agents were ergometrine plus oxytocin and ergometrine.

Figure 32. Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for vomiting.
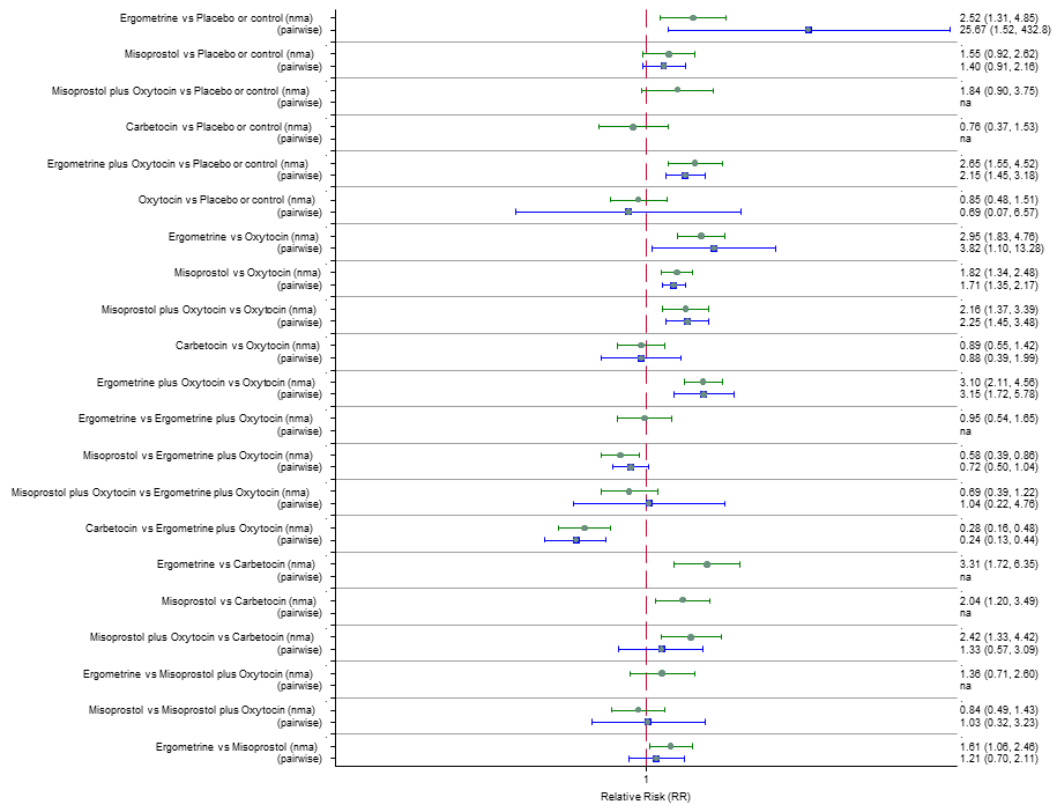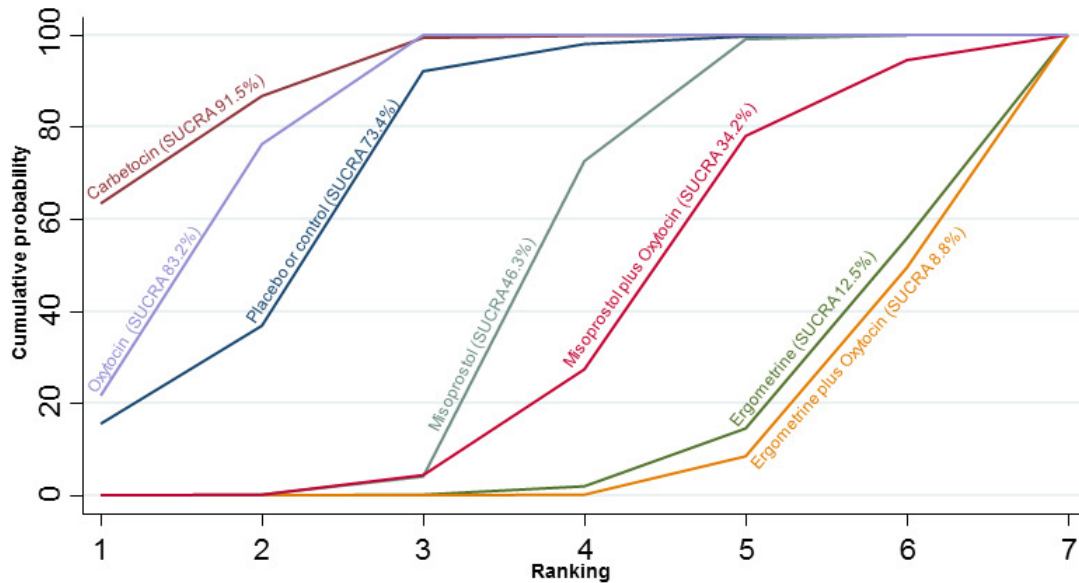
Figure 33. Cumulative rankograms comparing each of the uterotonic drugs for vomiting.

Hypertension

The network diagram for hypertension is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 15 trials suggested that ergometrine is worse than placebo or no treatment in causing hypertension (Figure 34). Ergometrine was found to be worse in causing hypertension when compared with the standard agent oxytocin (Figure 34). Ergometrine was also significantly worse in causing hypertension than carbetocin and misoprostol. There was no evidence of global inconsistency in this analysis (P = 0.481). Figure 35 shows the cumulative probabilities for each agent being at each possible rank for causing hypertension. The lowest ranked agents were ergometrine and ergometrine plus oxytocin. However, not all agents could be ranked because of too few studies in this analysis.

Figure 34.   Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for hypertension.
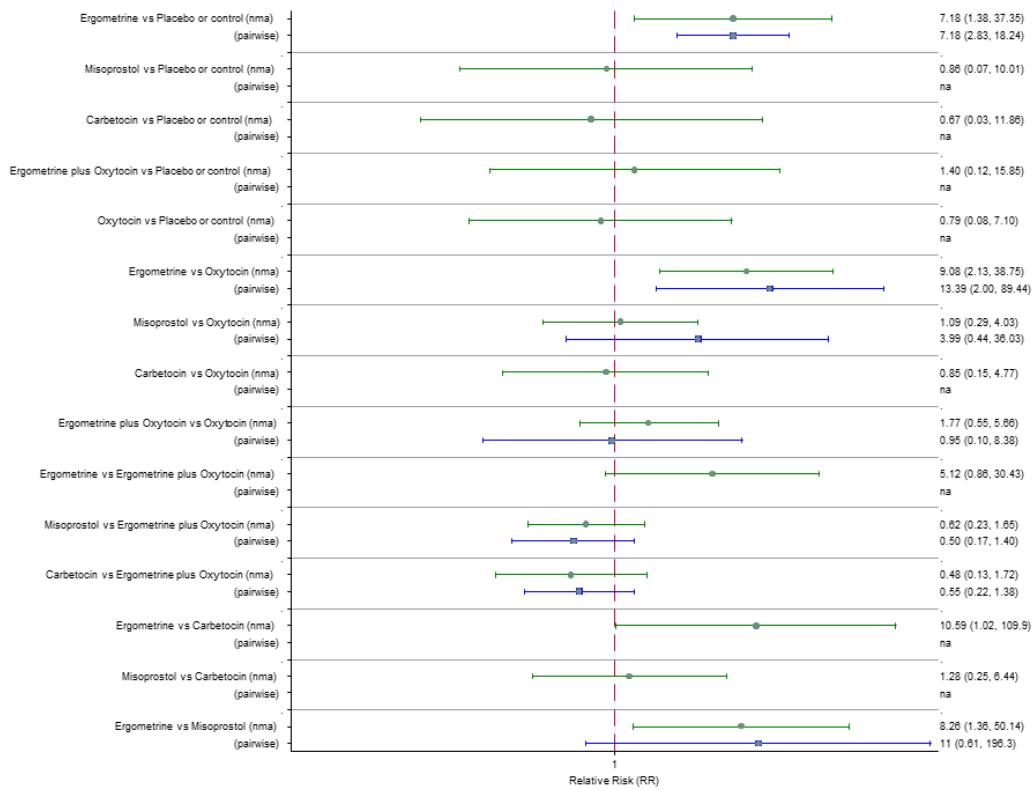

Ergometrine vs Placebo or control (nma)	7.18 (1.38, 37.35)
(pairwise)	7.18 (2.83, 18.24)
Misoprostol vs Placebo or control (nma)	0.86 (0.07, 10.01)
(pairwise)	na
Carbetocin vs Placebo or control (nma)	0.67 (0.03, 11.86)
(pairwise)	na
Ergometrine plus Oxytocin vs Placebo or control (nma)	1.40 (0.12, 15.85)
(pairwise)	na
Oxytocin vs Placebo or control (nma)	0.79 (0.08, 7.10)
(pairwise)	na
Ergometrine vs Oxytocin (nma)	9.08 (2.13, 38.75)
(pairwise)	13.39 (2.00, 89.44)
Misoprostol vs Oxytocin (nma)	1.09 (0.29, 4.03)
(pairwise)	3.99 (0.44, 36.03)
Carbetocin vs Oxytocin (nma)	0.85 (0.15, 4.77)
(pairwise)	na
Ergometrine plus Oxytocin vs Oxytocin (nma)	1.77 (0.55, 5.66)
(pairwise)	0.95 (0.10, 8.38)
Ergometrine vs Ergometrine plus Oxytocin (nma)	5.12 (0.86, 30.43)
(pairwise)	na
Misoprostol vs Ergometrine plus Oxytocin (nma)	0.62 (0.23, 1.65)
(pairwise)	0.50 (0.17, 1.40)
Carbetocin vs Ergometrine plus Oxytocin (nma)	0.48 (0.13, 1.72)
(pairwise)	0.55 (0.22, 1.38)
Ergometrine vs Carbetocin (nma)	10.59 (1.02, 109.9)
(pairwise)	na
Misoprostol vs Carbetocin (nma)	1.28 (0.25, 6.44)
(pairwise)	na
Ergometrine vs Misoprostol (nma)	8.26 (1.36, 50.14)
(pairwise)	11 (0.61, 196.3)

Relative Risk (RR)

Figure 35. Cumulative rankograms comparing each of the uterotonic drugs for hypertension.
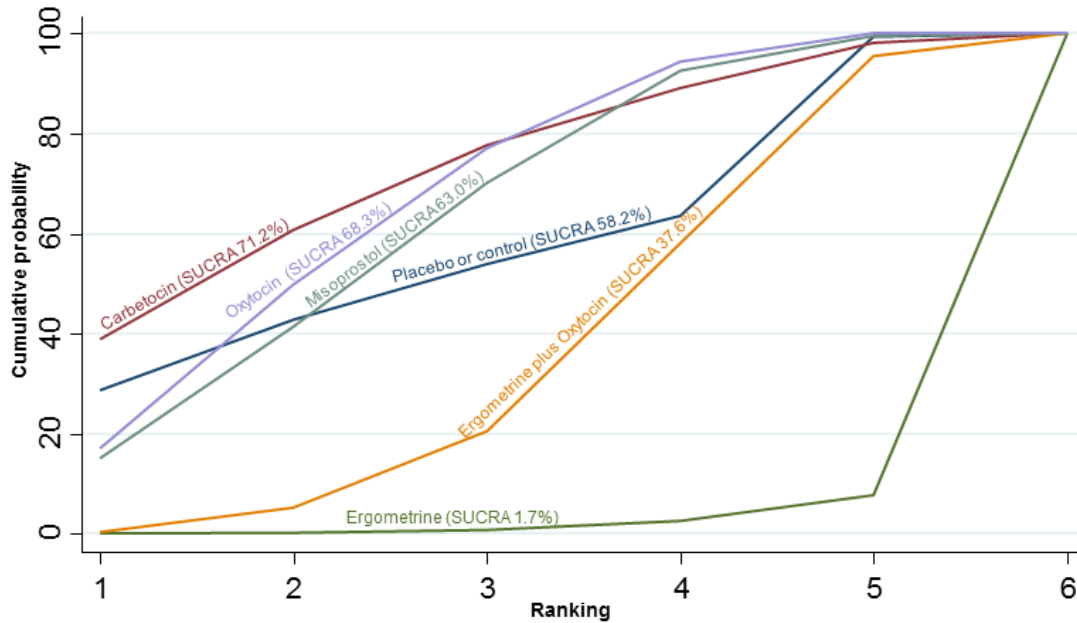
Headache

The network diagram for headache is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 45 trials suggested that ergometrine is worse than placebo or no treatment in causing headache (Figure 36). Ergometrine was found to be worse in causing headache when compared with the standard agent oxytocin (Figure 36). Ergometrine was also significantly worse in causing headache than carbetocin and misoprostol. There was no evidence of global inconsistency in this analysis (P = 0.826). Figure 37 shows the cumulative probabilities for each agent being at each possible rank for causing headache. The lowest ranked agents were ergometrine, misoprostol plus oxytocin and ergometrine plus oxytocin. The highest ranked agents were placebo or no treatment, carbetocin and oxytocin.

Figure 36.   Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for headache.
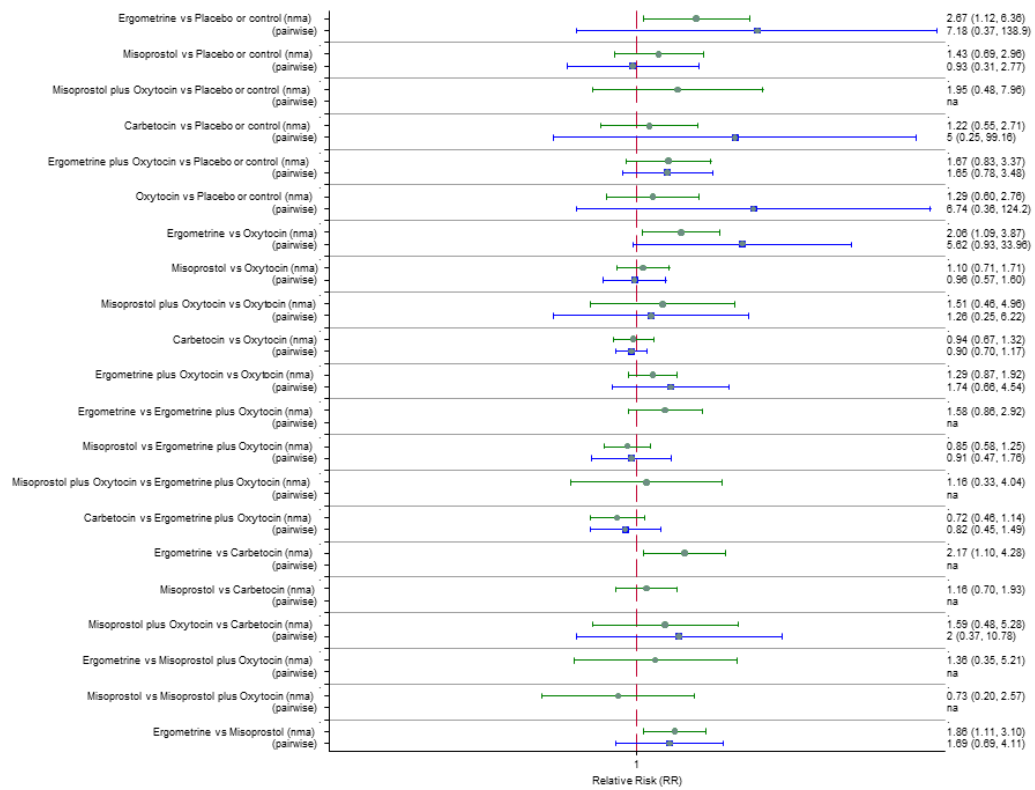

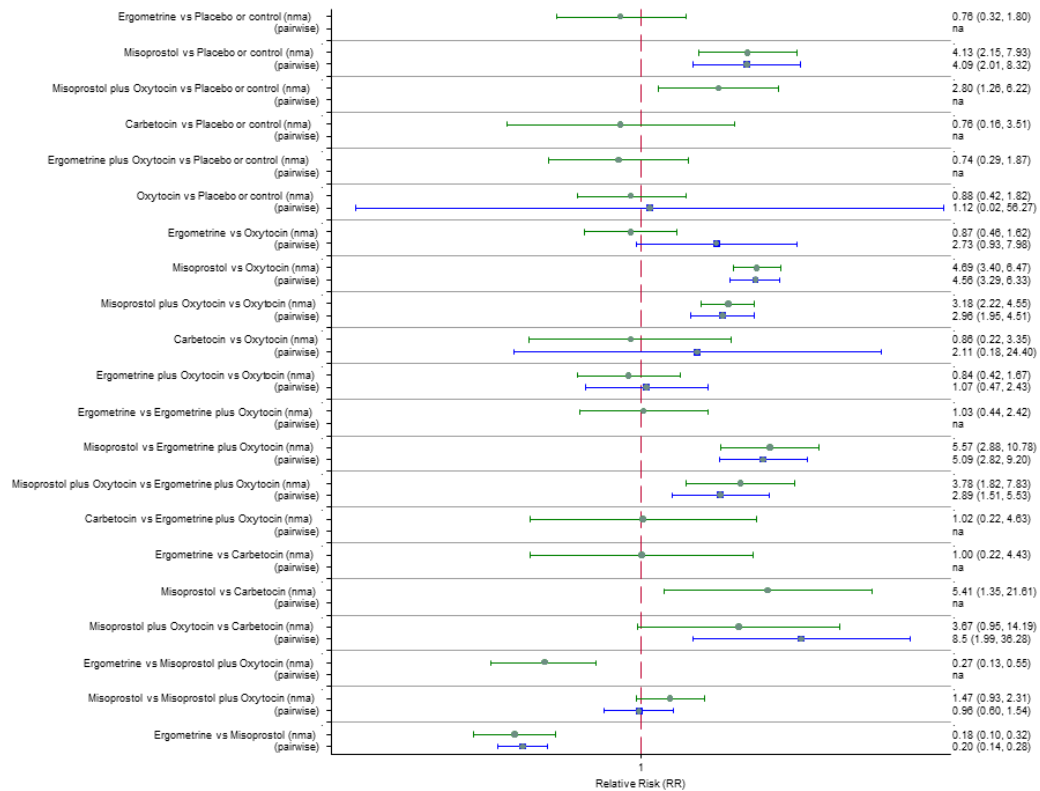|		RR (95% CI)
Ergometrine vs Placebo or control	(nma)	2.67 (1.12, 6.36)
	(pairwise)	7.18 (0.37, 138.9)
Misoprostol vs Placebo or control	(nma)	1.43 (0.69, 2.96)
	(pairwise)	0.93 (0.31, 2.77)
Misoprostol plus Oxytocin vs Placebo or control	(nma)	1.95 (0.48, 7.96)
	(pairwise)	na
Carbetocin vs Placebo or control	(nma)	1.22 (0.55, 2.71)
	(pairwise)	5 (0.25, 99.16)
Ergometrine plus Oxytocin vs Placebo or control	(nma)	1.67 (0.83, 3.37)
	(pairwise)	1.65 (0.78, 3.48)
Oxytocin vs Placebo or control	(nma)	1.29 (0.60, 2.76)
	(pairwise)	6.74 (0.36, 124.2)
Ergometrine vs Oxytocin	(nma)	2.06 (1.09, 3.87)
	(pairwise)	5.62 (0.93, 33.96)
Misoprostol vs Oxytocin	(nma)	1.10 (0.71, 1.71)
	(pairwise)	0.96 (0.57, 1.60)
Misoprostol plus Oxytocin vs Oxytocin	(nma)	1.51 (0.46, 4.96)
	(pairwise)	1.26 (0.25, 6.22)
Carbetocin vs Oxytocin	(nma)	0.94 (0.67, 1.32)
	(pairwise)	0.90 (0.70, 1.17)
Ergometrine plus Oxytocin vs Oxytocin	(nma)	1.29 (0.87, 1.92)
	(pairwise)	1.74 (0.66, 4.54)
Ergometrine vs Ergometrine plus Oxytocin	(nma)	1.58 (0.86, 2.92)
	(pairwise)	na
Misoprostol vs Ergometrine plus Oxytocin	(nma)	0.85 (0.58, 1.25)
	(pairwise)	0.91 (0.47, 1.76)
Misoprostol plus Oxytocin vs Ergometrine plus Oxytocin	(nma)	1.16 (0.33, 4.04)
	(pairwise)	na
Carbetocin vs Ergometrine plus Oxytocin	(nma)	0.72 (0.46, 1.14)
	(pairwise)	0.82 (0.45, 1.49)
Ergometrine vs Carbetocin	(nma)	2.17 (1.10, 4.28)
	(pairwise)	na
Misoprostol vs Carbetocin	(nma)	1.16 (0.70, 1.93)
	(pairwise)	na
Misoprostol plus Oxytocin vs Carbetocin	(nma)	1.59 (0.48, 5.28)
	(pairwise)	2 (0.37, 10.78)
Ergometrine vs Misoprostol plus Oxytocin	(nma)	1.36 (0.35, 5.21)
	(pairwise)	na
Misoprostol vs Misoprostol plus Oxytocin	(nma)	0.73 (0.20, 2.57)
	(pairwise)	na
Ergometrine vs Misoprostol	(nma)	1.86 (1.11, 3.10)
	(pairwise)	1.69 (0.69, 4.11)

1
Relative Risk (RR)

Figure 37.   Cumulative rankograms comparing each of the uterotonic drugs for headache.
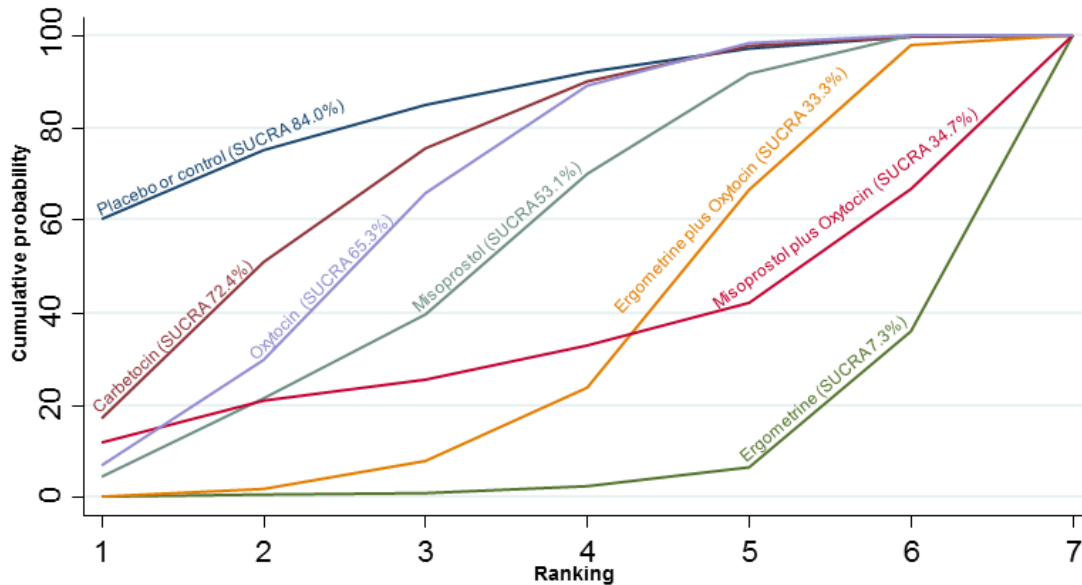
Fever

The network diagram for fever is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 64 trials suggested that misoprostol and misoprostol plus oxytocin are worse than placebo or no treatment in causing fever (Figure 38). Misoprostol and misoprostol plus oxytocin were found to be worse in causing fever when compared with the standard agent oxytocin (Figure 38). Misoprostol and misoprostol plus oxytocin were also significantly worse in causing fever than carbetocin, ergometrine

and ergometrine plus oxytocin with the exception of the comparison carbetocin versus misoprostol plus oxytocin which fell just short of being statistically significant. There was no evidence of global inconsistency in this analysis (P = 0.352). Figure 39 shows the cumulative probabilities for each agent being at each possible rank for causing fever. The highest ranked agents were carbetocin, oxytocin and placebo or no treatment. The lowest ranked agents were misoprostol and misoprostol plus oxytocin. The rest of the agents were similar in ranking to the placebo or no treatment group.

Figure 38. Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for fever.


|	
Ergometrine vs Placebo or control (nma) (pairwise)	0.76 (0.32, 1.80) na
Misoprostol vs Placebo or control (nma) (pairwise)	4.13 (2.15, 7.93) 4.09 (2.01, 8.32)
Misoprostol plus Oxytocin vs Placebo or control (nma) (pairwise)	2.80 (1.26, 6.22) na
Carbetocin vs Placebo or control (nma) (pairwise)	0.76 (0.16, 3.51) na
Ergometrine plus Oxytocin vs Placebo or control (nma) (pairwise)	0.74 (0.29, 1.87) na
Oxytocin vs Placebo or control (nma) (pairwise)	0.88 (0.42, 1.82) 1.12 (0.02, 56.27)
Ergometrine vs Oxytocin (nma) (pairwise)	0.87 (0.46, 1.62) 2.73 (0.93, 7.98)
Misoprostol vs Oxytocin (nma) (pairwise)	4.69 (3.40, 6.47) 4.56 (3.29, 6.33)
Misoprostol plus Oxytocin vs Oxytocin (nma) (pairwise)	3.18 (2.22, 4.55) 2.96 (1.95, 4.51)
Carbetocin vs Oxytocin (nma) (pairwise)	0.86 (0.22, 3.35) 2.11 (0.18, 24.40)
Ergometrine plus Oxytocin vs Oxytocin (nma) (pairwise)	0.84 (0.42, 1.67) 1.07 (0.47, 2.43)
Ergometrine vs Ergometrine plus Oxytocin (nma) (pairwise)	1.03 (0.44, 2.42) na
Misoprostol vs Ergometrine plus Oxytocin (nma) (pairwise)	5.57 (2.88, 10.78) 5.09 (2.82, 9.20)
Misoprostol plus Oxytocin vs Ergometrine plus Oxytocin (nma) (pairwise)	3.78 (1.82, 7.83) 2.89 (1.51, 5.53)
Carbetocin vs Ergometrine plus Oxytocin (nma) (pairwise)	1.02 (0.22, 4.63) na
Ergometrine vs Carbetocin (nma) (pairwise)	1.00 (0.22, 4.43) na
Misoprostol vs Carbetocin (nma) (pairwise)	5.41 (1.35, 21.61) na
Misoprostol plus Oxytocin vs Carbetocin (nma) (pairwise)	3.67 (0.95, 14.19) 8.5 (1.99, 36.28)
Ergometrine vs Misoprostol plus Oxytocin (nma) (pairwise)	0.27 (0.13, 0.55) na
Misoprostol vs Misoprostol plus Oxytocin (nma) (pairwise)	1.47 (0.93, 2.31) 0.96 (0.60, 1.54)
Ergometrine vs Misoprostol (nma) (pairwise)	0.18 (0.10, 0.32) 0.20 (0.14, 0.28)

Relative Risk (RR)

Figure 39. Cumulative rankograms comparing each of the uterotonic drugs for fever.
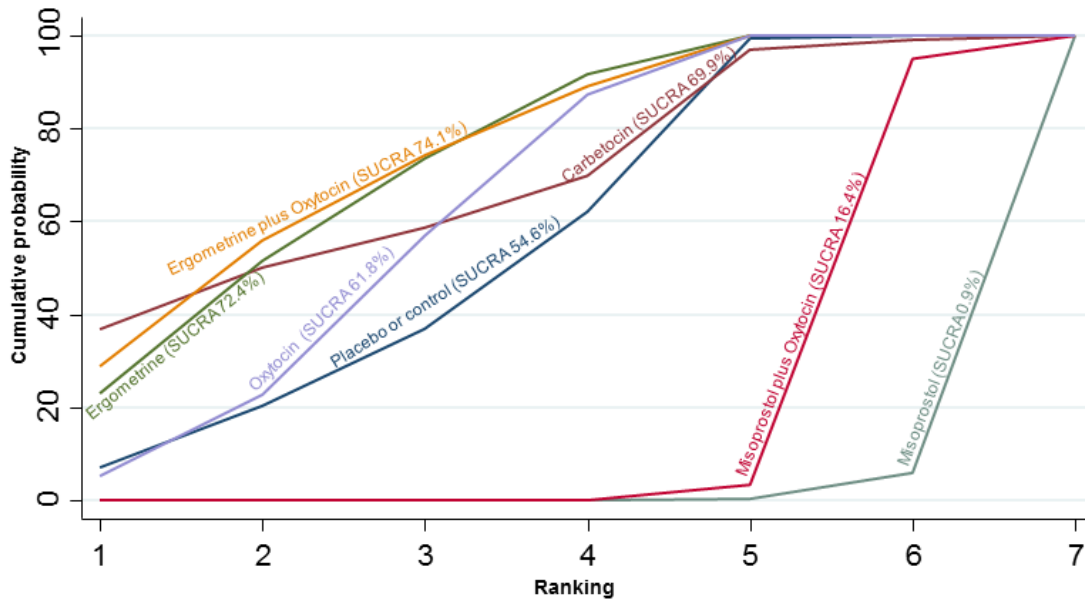
Shivering

The network diagram for shivering is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 87 trials suggested that misoprostol and misoprostol plus oxytocin are worse than placebo or no treatment in causing shivering (Figure 40). Misoprostol and misoprostol plus oxytocin were found to be worse in causing shivering when compared with the standard agent oxytocin (Figure 40). Misoprostol and misoprostol plus oxy-

tocin were also significantly worse in causing shivering than carbetocin, ergometrine and ergometrine plus oxytocin. There was no evidence of global inconsistency in this analysis (P = 0.923). Figure 41 shows the cumulative probabilities for each agent being at each possible rank for causing shivering. The highest ranked agents were carbetocin and oxytocin. The lowest ranked agents were misoprostol and misoprostol plus oxytocin. Ergometrine and ergometrine plus oxytocin were similar in ranking to the placebo or no treatment group.

Figure 40.   Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for shivering.
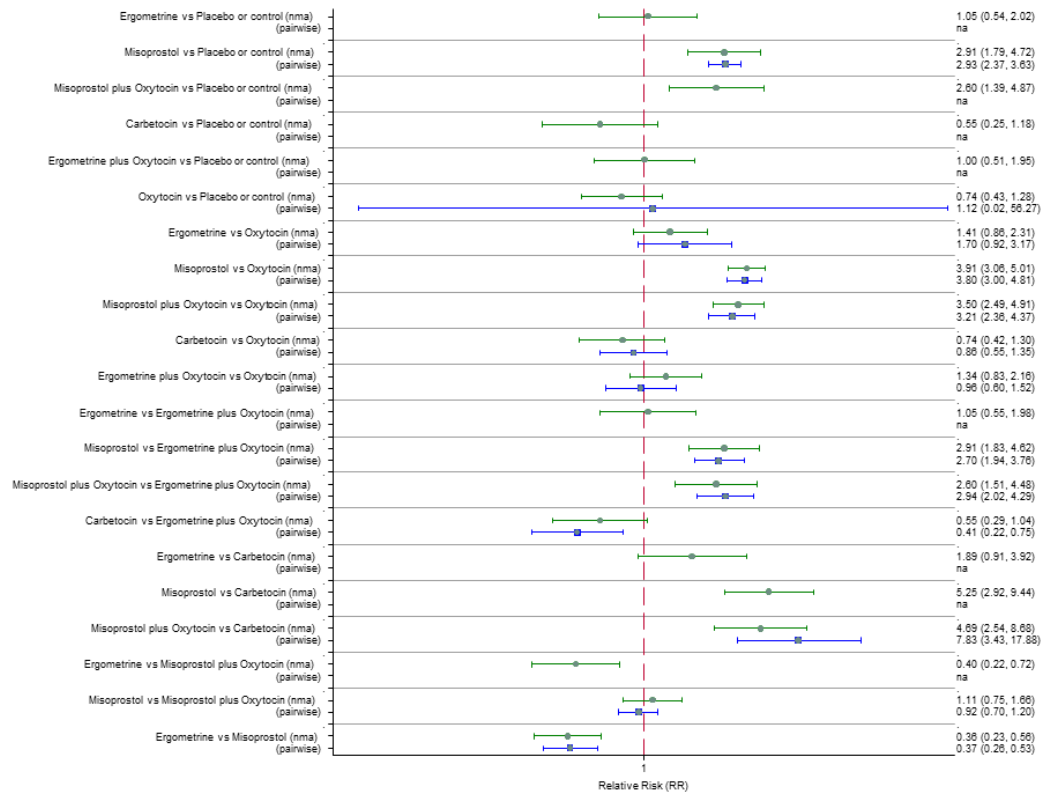
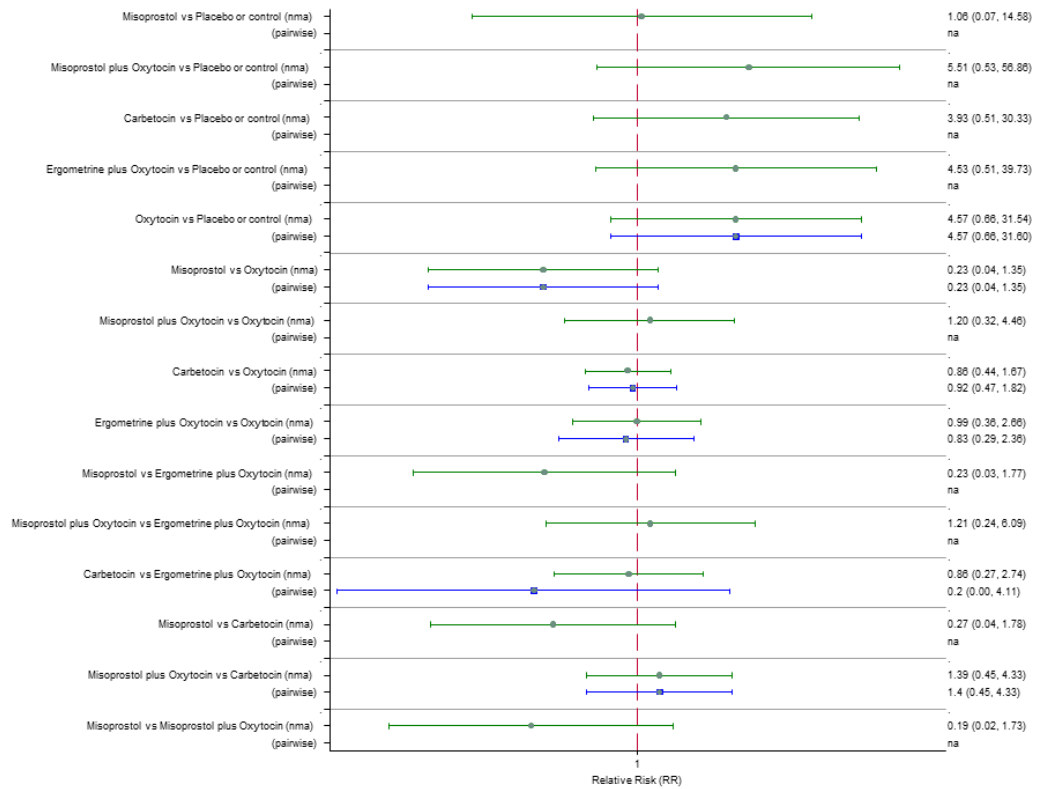**Figure 41. Cumulative rankograms comparing each of the uterotonic drugs for shivering.**
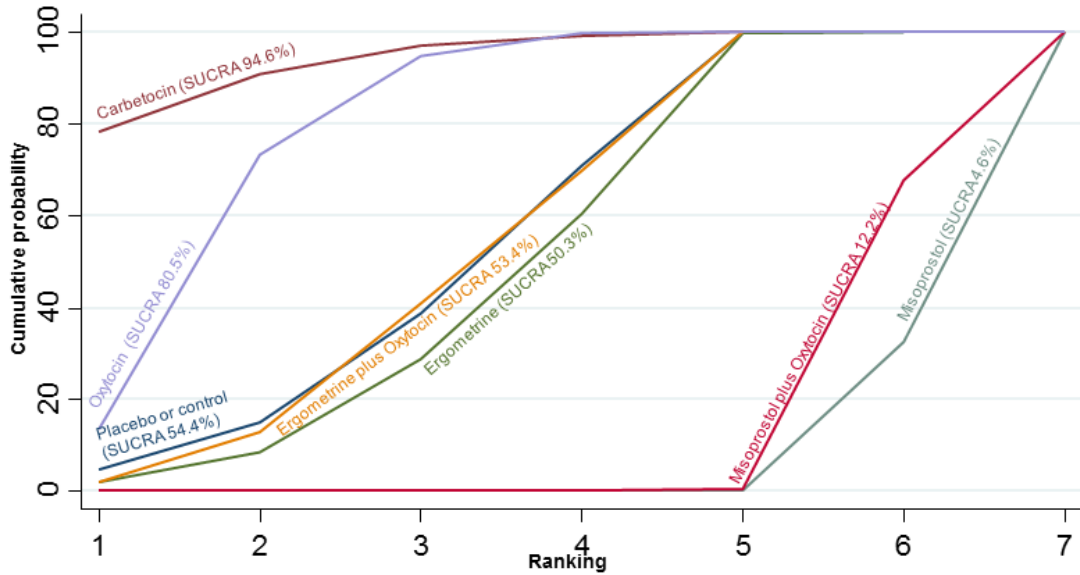
Tachycardia

The network diagram for tachycardia is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of seven trials suggested only that carbetocin is worse than oxytocin and ergometrine plus oxytocin in causing tachycardia, but most of the comparisons were based on single studies (Figure 42). There was no evidence of global inconsistency in this analysis (P = 0.361). Figure 43 shows the cumulative probabilities for each agent being at each possible rank for causing tachycardia. No clear ranking emerged and not all agents could be ranked because of the lack of studies in this analysis.

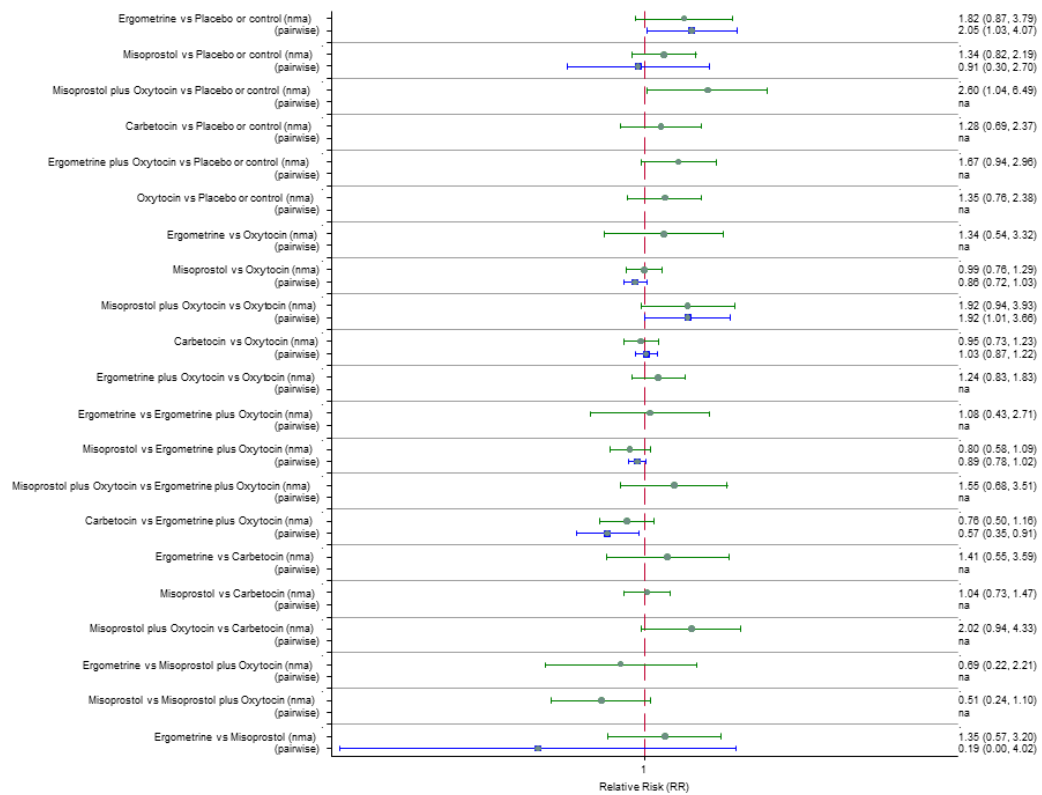**Figure 42. Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for tachycardia.**
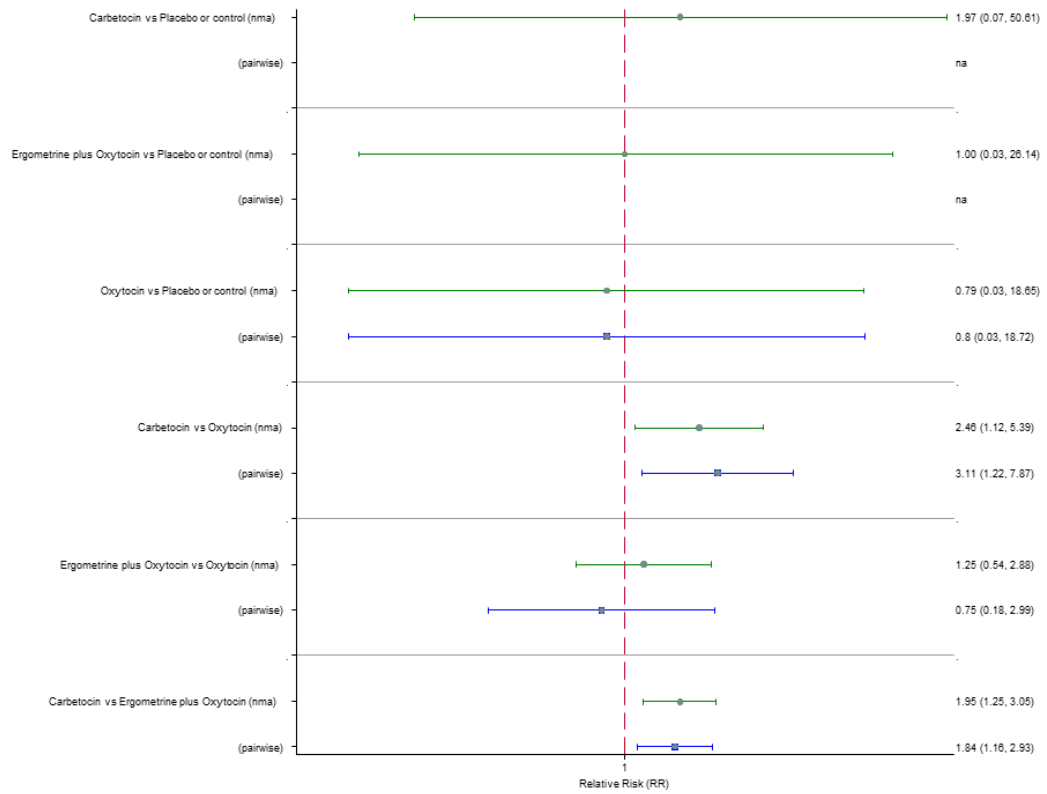
Figure 43. Cumulative rankograms comparing each of the uterotonic drugs for tachycardia.
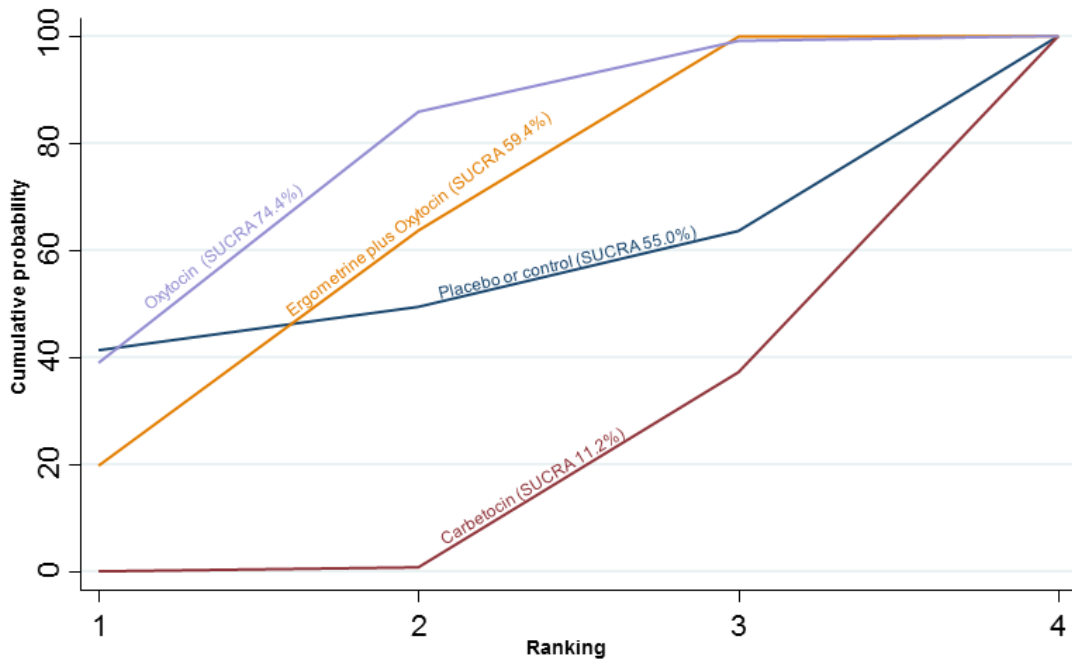
Hypotension

The network diagram for hypotension is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 8 trials suggested a lack of evidence that any agent is worse or better than any other as most of the comparisons were based on single studies (Figure 44). There was no evidence of global inconsistency in this analysis (P = 0.304). Figure 45 shows the cumulative probabilities for each agent being at each possible rank for causing hypotension. The highest ranked agents were misoprostol and placebo or no treatment. For the rest of the agents no clear ranking emerged and not all agents could be ranked because of the lack of studies in this analysis.

Figure 44.   Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for hypotension.

Misoprostol vs Placebo or control (nma)	1.06 (0.07, 14.58)
(pairwise)	na
Misoprostol plus Oxytocin vs Placebo or control (nma)	5.51 (0.53, 56.86)
(pairwise)	na
Carbetocin vs Placebo or control (nma)	3.93 (0.51, 30.33)
(pairwise)	na
Ergometrine plus Oxytocin vs Placebo or control (nma)	4.53 (0.51, 39.73)
(pairwise)	na
Oxytocin vs Placebo or control (nma)	4.57 (0.66, 31.54)
(pairwise)	4.57 (0.66, 31.60)
Misoprostol vs Oxytocin (nma)	0.23 (0.04, 1.35)
(pairwise)	0.23 (0.04, 1.35)
Misoprostol plus Oxytocin vs Oxytocin (nma)	1.20 (0.32, 4.46)
(pairwise)	na
Carbetocin vs Oxytocin (nma)	0.86 (0.44, 1.67)
(pairwise)	0.92 (0.47, 1.82)
Ergometrine plus Oxytocin vs Oxytocin (nma)	0.99 (0.36, 2.66)
(pairwise)	0.83 (0.29, 2.36)
Misoprostol vs Ergometrine plus Oxytocin (nma)	0.23 (0.03, 1.77)
(pairwise)	na
Misoprostol plus Oxytocin vs Ergometrine plus Oxytocin (nma)	1.21 (0.24, 6.09)
(pairwise)	na
Carbetocin vs Ergometrine plus Oxytocin (nma)	0.86 (0.27, 2.74)
(pairwise)	0.2 (0.00, 4.11)
Misoprostol vs Carbetocin (nma)	0.27 (0.04, 1.78)
(pairwise)	na
Misoprostol plus Oxytocin vs Carbetocin (nma)	1.39 (0.45, 4.33)
(pairwise)	1.4 (0.45, 4.33)
Misoprostol vs Misoprostol plus Oxytocin (nma)	0.19 (0.02, 1.73)
(pairwise)	na

1
Relative Risk (RR)

Figure 45.   Cumulative rankograms comparing each of the uterotonic drugs for hypotension.
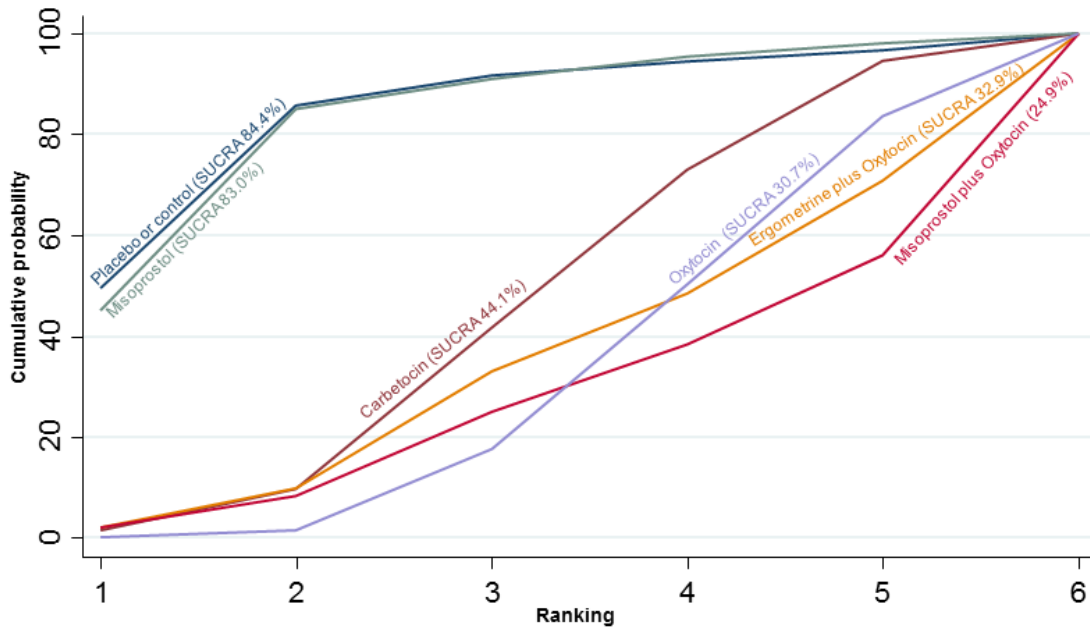
Abdominal pain

The network diagram for abdominal pain is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 25 trials suggested that misoprostol plus oxytocin is worse than placebo or no treatment in causing abdominal pain (Figure 46). No active agent was found to be worse or better than any other. There was evidence of global inconsistency in this analysis (P = 0.035). However, we note that the CIs for both the network meta-analysis and direct evidence were overlapping across all comparisons suggesting locally fairly consistent results. Figure 47 shows the cumulative probabilities for each agent being at each possible rank for causing abdominal pain. The highest ranked agent was placebo or no treatment. For the rest of the agents no clear ranking emerged because of the lack of studies in this analysis.

Figure 46.   Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for abdominal pain.

Ergometrine vs Placebo or control (nma)	1.82 (0.87, 3.79)
(pairwise)	2.05 (1.03, 4.07)
Misoprostol vs Placebo or control (nma)	1.34 (0.82, 2.19)
(pairwise)	0.91 (0.30, 2.70)
Misoprostol plus Oxytocin vs Placebo or control (nma)	2.60 (1.04, 6.49)
(pairwise)	na
Carbetocin vs Placebo or control (nma)	1.28 (0.69, 2.37)
(pairwise)	na
Ergometrine plus Oxytocin vs Placebo or control (nma)	1.67 (0.94, 2.96)
(pairwise)	na
Oxytocin vs Placebo or control (nma)	1.35 (0.76, 2.38)
(pairwise)	na
Ergometrine vs Oxytocin (nma)	1.34 (0.54, 3.32)
(pairwise)	na
Misoprostol vs Oxytocin (nma)	0.99 (0.76, 1.29)
(pairwise)	0.86 (0.72, 1.03)
Misoprostol plus Oxytocin vs Oxytocin (nma)	1.92 (0.94, 3.93)
(pairwise)	1.92 (1.01, 3.66)
Carbetocin vs Oxytocin (nma)	0.95 (0.73, 1.23)
(pairwise)	1.03 (0.87, 1.22)
Ergometrine plus Oxytocin vs Oxytocin (nma)	1.24 (0.83, 1.83)
(pairwise)	na
Ergometrine vs Ergometrine plus Oxytocin (nma)	1.08 (0.43, 2.71)
(pairwise)	na
Misoprostol vs Ergometrine plus Oxytocin (nma)	0.80 (0.58, 1.09)
(pairwise)	0.89 (0.78, 1.02)
Misoprostol plus Oxytocin vs Ergometrine plus Oxytocin (nma)	1.55 (0.68, 3.51)
(pairwise)	na
Carbetocin vs Ergometrine plus Oxytocin (nma)	0.76 (0.50, 1.16)
(pairwise)	0.57 (0.35, 0.91)
Ergometrine vs Carbetocin (nma)	1.41 (0.55, 3.59)
(pairwise)	na
Misoprostol vs Carbetocin (nma)	1.04 (0.73, 1.47)
(pairwise)	na
Misoprostol plus Oxytocin vs Carbetocin (nma)	2.02 (0.94, 4.33)
(pairwise)	na
Ergometrine vs Misoprostol plus Oxytocin (nma)	0.69 (0.22, 2.21)
(pairwise)	na
Misoprostol vs Misoprostol plus Oxytocin (nma)	0.51 (0.24, 1.10)
(pairwise)	na
Ergometrine vs Misoprostol (nma)	1.35 (0.57, 3.20)
(pairwise)	0.19 (0.00, 4.02)

Relative Risk (RR)

Figure 47. Cumulative rankograms comparing each of the uterotonic drugs for abdominal pain.
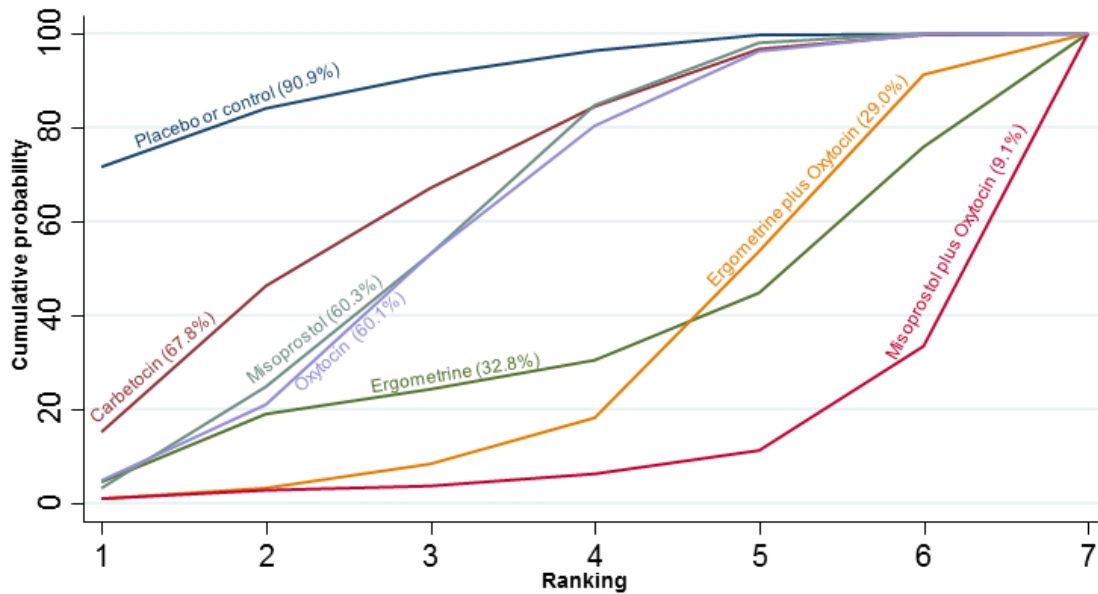
Subgroup analyses

Mode of birth

Vaginal birth

PPH ≥ 500 mL

The network diagram for PPH ≥ 500 mL for the subgroup including only vaginal births is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 85 trials suggested that all agents are effective for preventing PPH ≥ 500 mL when compared with placebo or no treatment (Figure 48). Ergometrine plus oxytocin, and misoprostol plus oxytocin were found to be more effective when compared with the standard agent oxytocin. Carbetocin also demonstrated a trend towards reduction of this outcome (Figure 48). Ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin were also found to be more effective when compared with misoprostol and ergometrine when used alone. There was no evidence of global inconsistency in this analysis (P = 0.06). Figure 49 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 500 mL for the subgroup including only vaginal births. The highest ranked agents were ergometrine plus oxytocin, carbetocin, and misoprostol plus oxytocin with an almost 100% probability of these three agents being ranked first, second or third. Oxytocin was ranked fourth and its probability of being ranked in the top three agents was close to 0%.

Figure 48. Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for prevention of PPH ≥ 500 mL by mode of birth (vaginal birth).
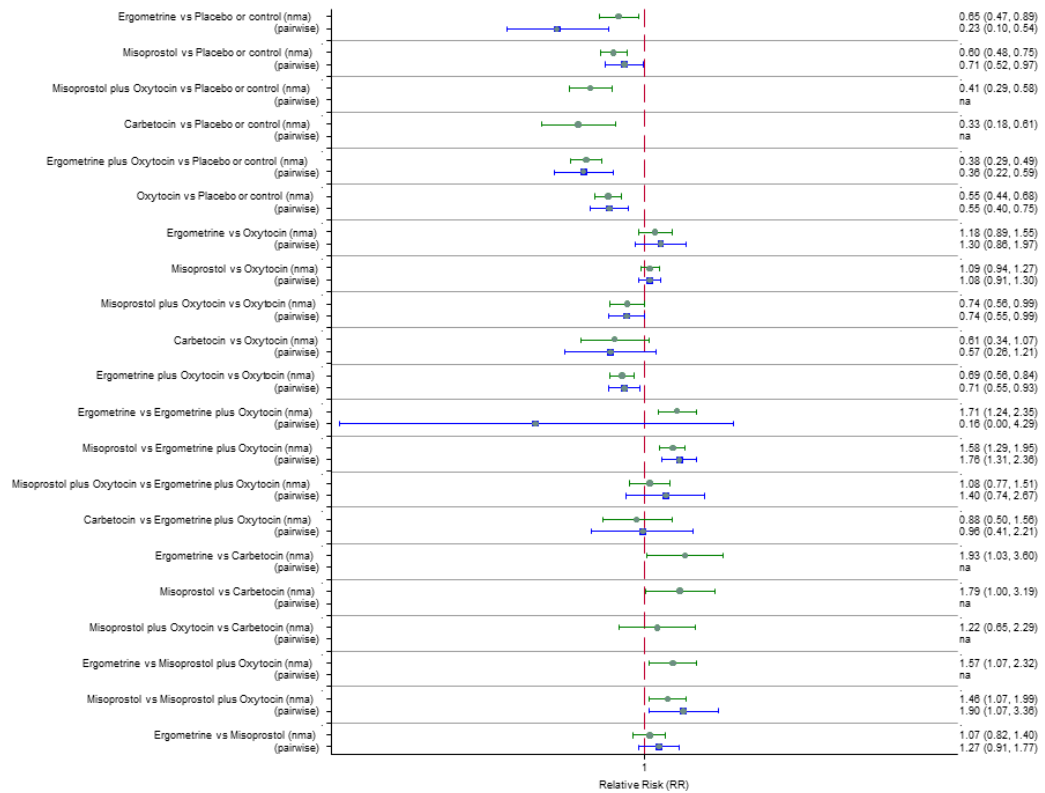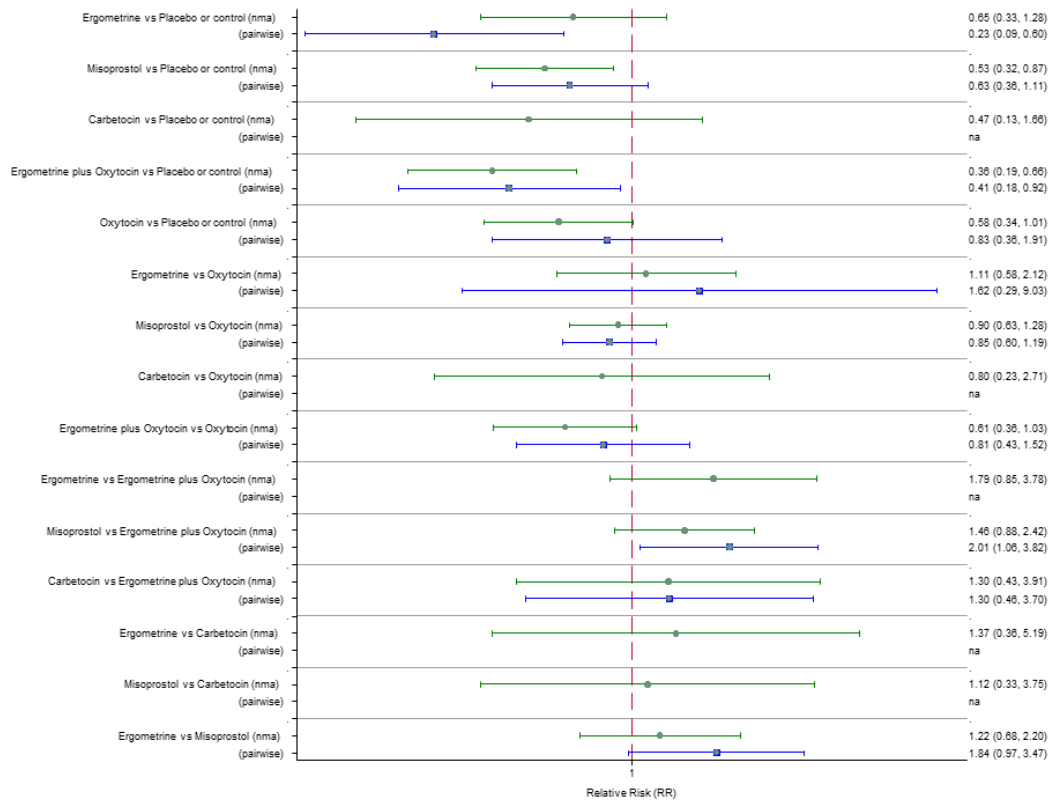
Figure 49. Cumulative rankograms comparing each of the uterotonic drugs for prevention of PPH ≥ 500 mL by mode of birth (vaginal birth).
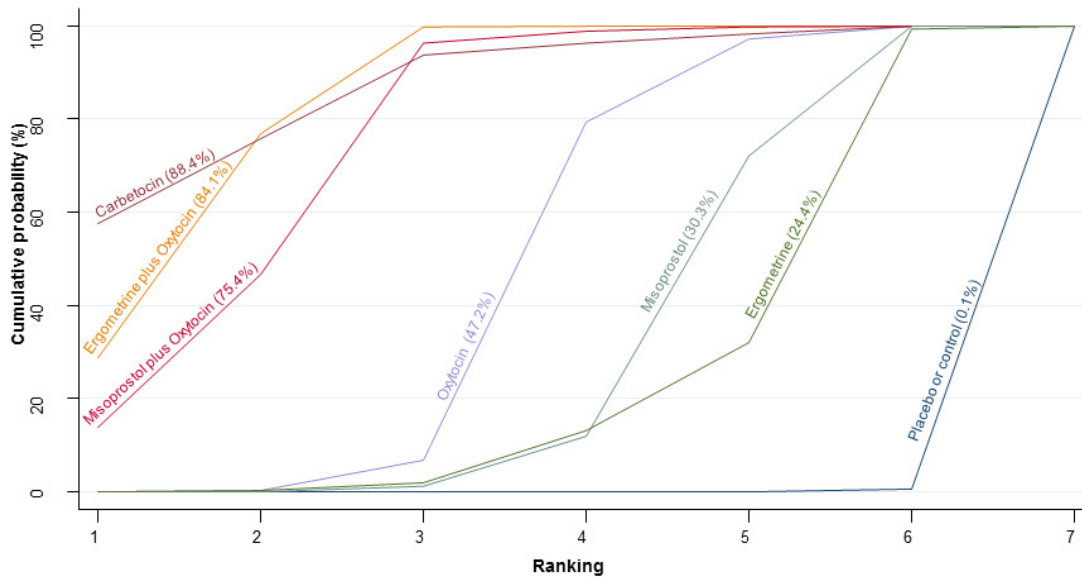
PPH ≥ 1000 mL

Pooled effect estimates from the network meta-analysis of 71 trials suggested that all agents except carbetocin and ergometrine are effective for preventing PPH ≥ 1000 mL when compared with placebo or no treatment (Appendix 3). Ergometrine plus oxytocin was the only agent found to be more effective when compared with the standard agent oxytocin. Carbetocin and misoprostol plus oxytocin demonstrated a trend towards reduction of this outcome (Appendix 3). There was no evidence of global inconsistency in this analysis (P = 0.206). Appendix 3 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 1000 mL for the subgroup including only vaginal births. The highest ranked agents were carbetocin, ergometrine plus oxytocin, and misoprostol plus oxytocin. Oxytocin was ranked fourth and its probability in being ranked in the top two agents was close to 0%.

Caesarean section

PPH ≥ 500 mL

Pooled effect estimates from the network meta-analysis of 15 trials suggested that only misoprostol plus oxytocin is better than oxytocin alone in preventing PPH ≥ 500 mL for women undergoing caesareans, but most of the comparisons were based on single studies (Figure 50). There was no evidence of global inconsistency in this analysis (P = 0.249). Figure 51 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 500 mL for the subgroup including only caesareans. The highest ranked agents were misoprostol plus oxytocin and carbetocin. Oxytocin was ranked third and its probability in being ranked in the top two agents was close to 5%. Ergometrine and ergometrine plus oxytocin could not be ranked as there were no studies found comparing those with any other agents in the network.

Figure 50.   Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for prevention of PPH $\geq$ 500 mL by mode of birth (caesarean).
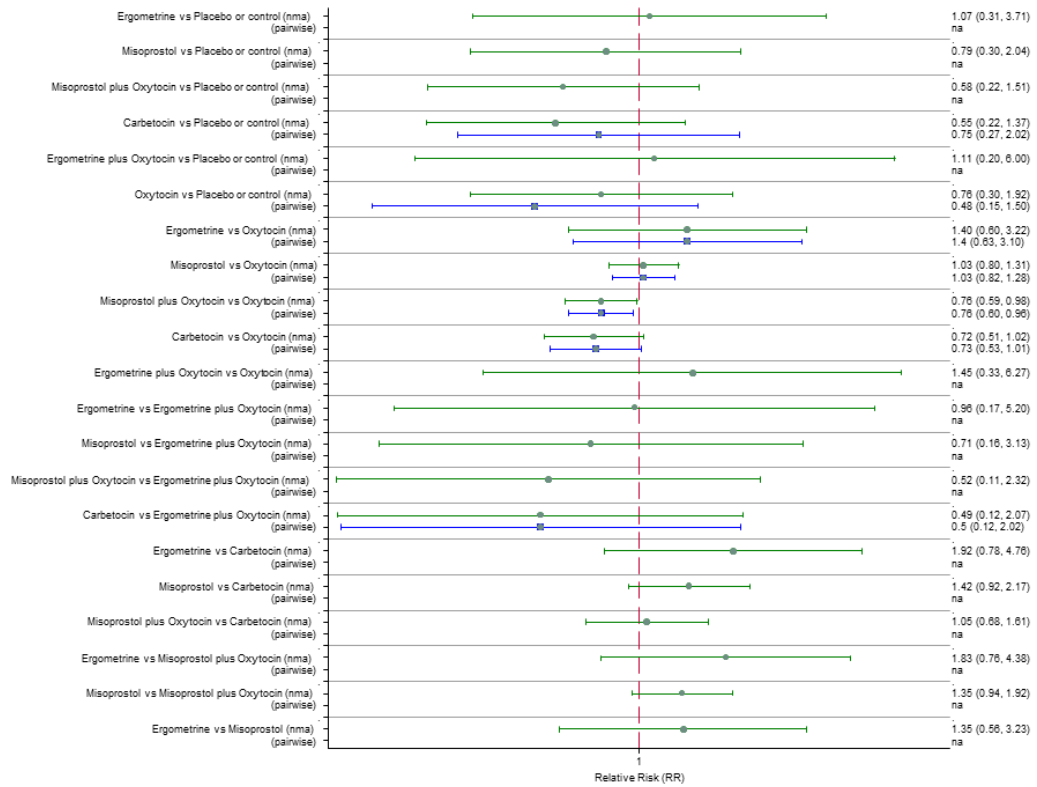

Misoprostol vs Placebo or control (nma)	0.75 (0.29, 1.95)
(pairwise)	na
Misoprostol plus Oxytocin vs Placebo or control (nma)	0.53 (0.20, 1.38)
(pairwise)	na
Carbetocin vs Placebo or control (nma)	0.57 (0.23, 1.41)
(pairwise)	0.75 (0.27, 2.01)
Oxytocin vs Placebo or control (nma)	0.73 (0.29, 1.84)
(pairwise)	0.48 (0.15, 1.50)
Misoprostol vs Oxytocin (nma)	1.03 (0.81, 1.31)
(pairwise)	1.03 (0.83, 1.27)
Misoprostol plus Oxytocin vs Oxytocin (nma)	0.72 (0.55, 0.94)
(pairwise)	0.72 (0.56, 0.92)
Carbetocin vs Oxytocin (nma)	0.77 (0.52, 1.14)
(pairwise)	0.78 (0.54, 1.12)
Misoprostol vs Carbetocin (nma)	1.32 (0.84, 2.09)
(pairwise)	na
Misoprostol plus Oxytocin vs Carbetocin (nma)	0.92 (0.58, 1.48)
(pairwise)	na
Misoprostol vs Misoprostol plus Oxytocin (nma)	1.42 (0.99, 2.05)
(pairwise)	na

Relative Risk (RR)

Figure 51. Cumulative rankograms comparing each of the uterotonic drugs for prevention of PPH ≥ 500 mL by mode of birth (caesarean).
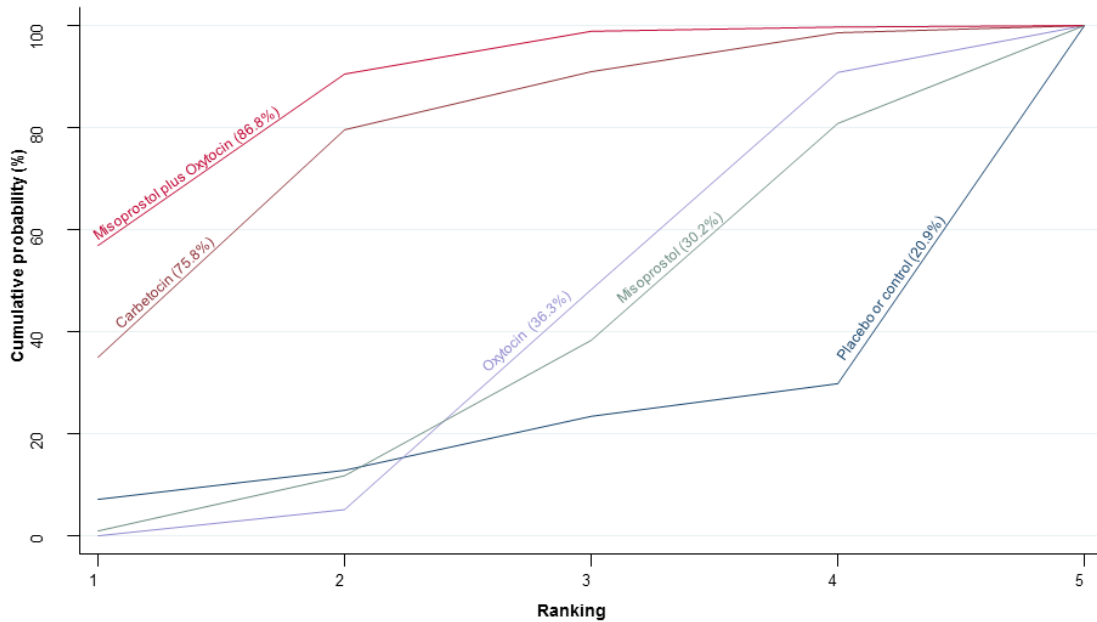
PPH ≥ 1000 mL

Pooled effect estimates from the network meta-analysis of 19 trials suggested a lack of evidence that any agent is worse or better than any other in preventing PPH ≥ 1000 mL in women undergoing caesareans, but many of the comparisons were based on single studies (Appendix 3). There was no evidence of global inconsistency in this analysis (P = 0.86). Appendix 3 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 1000 mL for the subgroup including only caesareans. No clear ranking emerged in this analysis. Ergometrine and ergometrine plus oxytocin could not be ranked as there were no studies found comparing those with any other agents in the network.

Prior risk of PPH

Low risk for PPH

PPH ≥ 500 mL

Pooled effect estimates from the network meta-analysis of 35 trials suggested that only ergometrine plus oxytocin and misoprostol are better than placebo or no treatment in preventing PPH ≥ 500 mL in women at low risk for PPH, but most of the comparisons were based on single studies (Figure 52). There was no evidence of global inconsistency in this analysis (P = 0.236). Figure 53 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 500 mL for the subgroup including only trials with women at low risk for PPH. The highest ranked agents were ergometrine plus oxytocin and carbetocin. Oxytocin was ranked fourth behind misoprostol and its probability in being ranked in the top two agents was close to 10%. Misoprostol plus oxytocin could not be ranked as there were no studies found comparing this agent with any other agents in the network.

Figure 52. Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for prevention of PPH ≥ 500 mL by prior risk for PPH (low risk).

Ergometrine vs Placebo or control (nma)		0.65 (0.33, 1.28)
(pairwise)		0.23 (0.09, 0.60)
Misoprostol vs Placebo or control (nma)		0.53 (0.32, 0.87)
(pairwise)		0.63 (0.36, 1.11)
Carbetocin vs Placebo or control (nma)		0.47 (0.13, 1.66)
(pairwise)		na
Ergometrine plus Oxytocin vs Placebo or control (nma)		0.36 (0.19, 0.66)
(pairwise)		0.41 (0.18, 0.92)
Oxytocin vs Placebo or control (nma)		0.58 (0.34, 1.01)
(pairwise)		0.83 (0.36, 1.91)
Ergometrine vs Oxytocin (nma)		1.11 (0.58, 2.12)
(pairwise)		1.62 (0.29, 9.03)
Misoprostol vs Oxytocin (nma)		0.90 (0.63, 1.28)
(pairwise)		0.85 (0.60, 1.19)
Carbetocin vs Oxytocin (nma)		0.80 (0.23, 2.71)
(pairwise)		na
Ergometrine plus Oxytocin vs Oxytocin (nma)		0.61 (0.36, 1.03)
(pairwise)		0.81 (0.43, 1.52)
Ergometrine vs Ergometrine plus Oxytocin (nma)		1.79 (0.85, 3.78)
(pairwise)		na
Misoprostol vs Ergometrine plus Oxytocin (nma)		1.46 (0.88, 2.42)
(pairwise)		2.01 (1.06, 3.82)
Carbetocin vs Ergometrine plus Oxytocin (nma)		1.30 (0.43, 3.91)
(pairwise)		1.30 (0.46, 3.70)
Ergometrine vs Carbetocin (nma)		1.37 (0.36, 5.19)
(pairwise)		na
Misoprostol vs Carbetocin (nma)		1.12 (0.33, 3.75)
(pairwise)		na
Ergometrine vs Misoprostol (nma)		1.22 (0.68, 2.20)
(pairwise)		1.84 (0.97, 3.47)

Relative Risk (RR)

Figure 53. Cumulative rankograms comparing each of the uterotonic drugs for prevention of PPH ≥ 500 mL by prior risk for PPH (low risk).
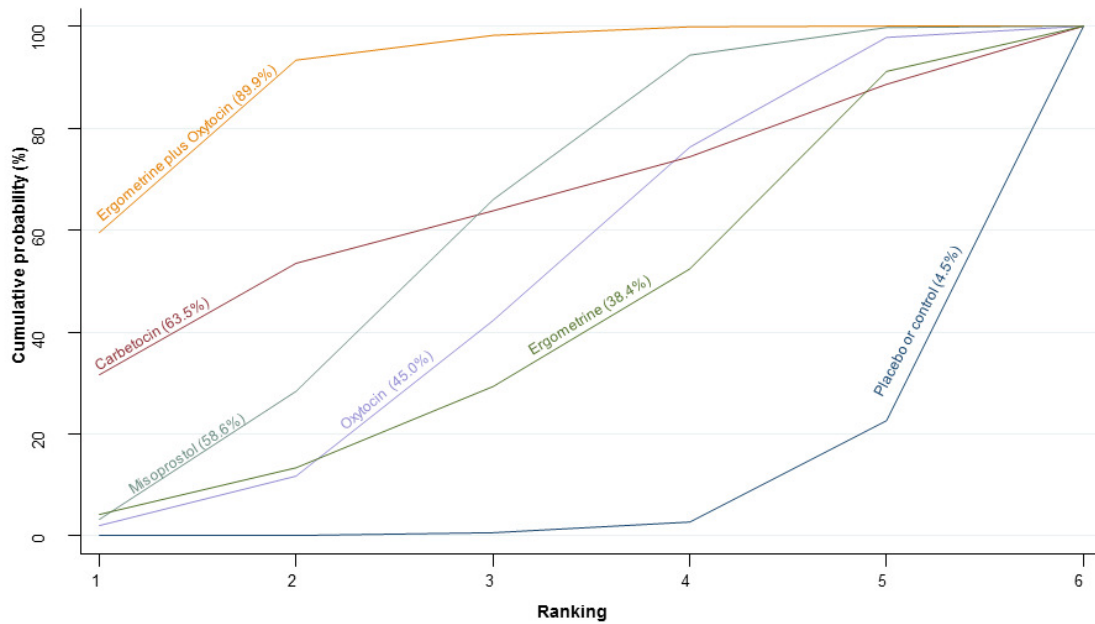
PPH ≥ 1000 mL

Pooled effect estimates from the network meta-analysis of 32 trials suggested that ergometrine plus oxytocin, oxytocin, ergometrine and misoprostol are better than placebo or no treatment in preventing PPH ≥ 1000 mL in women at low risk for PPH (Appendix 3). The comparisons between active agents appeared to be underpowered to detect differences between them. There was no evidence of global inconsistency in this analysis (P = 0.477). Appendix 3 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 1000 mL for the subgroup including only trials with women at low risk for PPH. No clear ranking emerged in this analysis. Ergometrine could not be ranked as there were no studies found comparing those with any other agents in the network.

High risk for PPH

PPH ≥ 500 mL

Pooled effect estimates from the network meta-analysis of 21 trials suggested that only isoprostol plus oxytocin is better than oxytocin in preventing PPH ≥ 500 mL and carbetocin showed a similar trend towards prevention of this outcome for women at high risk for PPH, but most of the comparisons were based on single studies (Figure 54). There was no evidence of global inconsistency in this analysis (P = 0.211). Figure 55 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 500 mL for the subgroup including only trials with women at high risk for PPH. The highest ranked agents were misoprostol plus oxytocin and carbetocin. Oxytocin was ranked third closely followed by misoprostol and its probability in being ranked in the top two agents was close to 0%.

Figure 54. Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for prevention of PPH ≥ 500 mL by prior risk for PPH (high risk).

Comparison	RR (95% CI)
Ergometrine vs Placebo or control (nma) / (pairwise)	1.07 (0.31, 3.71) / na
Misoprostol vs Placebo or control (nma) / (pairwise)	0.79 (0.30, 2.04) / na
Misoprostol plus Oxytocin vs Placebo or control (nma) / (pairwise)	0.58 (0.22, 1.51) / na
Carbetocin vs Placebo or control (nma) / (pairwise)	0.55 (0.22, 1.37) / 0.75 (0.27, 2.02)
Ergometrine plus Oxytocin vs Placebo or control (nma) / (pairwise)	1.11 (0.20, 6.00) / na
Oxytocin vs Placebo or control (nma) / (pairwise)	0.76 (0.30, 1.92) / 0.48 (0.15, 1.50)
Ergometrine vs Oxytocin (nma) / (pairwise)	1.40 (0.60, 3.22) / 1.4 (0.63, 3.10)
Misoprostol vs Oxytocin (nma) / (pairwise)	1.03 (0.80, 1.31) / 1.03 (0.82, 1.28)
Misoprostol plus Oxytocin vs Oxytocin (nma) / (pairwise)	0.76 (0.59, 0.98) / 0.76 (0.60, 0.96)
Carbetocin vs Oxytocin (nma) / (pairwise)	0.72 (0.51, 1.02) / 0.73 (0.53, 1.01)
Ergometrine plus Oxytocin vs Oxytocin (nma) / (pairwise)	1.45 (0.33, 6.27) / na
Ergometrine vs Ergometrine plus Oxytocin (nma) / (pairwise)	0.96 (0.17, 5.20) / na
Misoprostol vs Ergometrine plus Oxytocin (nma) / (pairwise)	0.71 (0.16, 3.13) / na
Misoprostol plus Oxytocin vs Ergometrine plus Oxytocin (nma) / (pairwise)	0.52 (0.11, 2.32) / na
Carbetocin vs Ergometrine plus Oxytocin (nma) / (pairwise)	0.49 (0.12, 2.07) / 0.5 (0.12, 2.02)
Ergometrine vs Carbetocin (nma) / (pairwise)	1.92 (0.78, 4.76) / na
Misoprostol vs Carbetocin (nma) / (pairwise)	1.42 (0.92, 2.17) / na
Misoprostol plus Oxytocin vs Carbetocin (nma) / (pairwise)	1.05 (0.68, 1.61) / na
Ergometrine vs Misoprostol plus Oxytocin (nma) / (pairwise)	1.83 (0.76, 4.38) / na
Misoprostol vs Misoprostol plus Oxytocin (nma) / (pairwise)	1.35 (0.94, 1.92) / na
Ergometrine vs Misoprostol (nma) / (pairwise)	1.35 (0.56, 3.23) / na

Relative Risk (RR)

Figure 55. Cumulative rankograms comparing each of the uterotonic drugs for prevention of PPH ≥ 500 mL by prior risk for PPH (high risk).
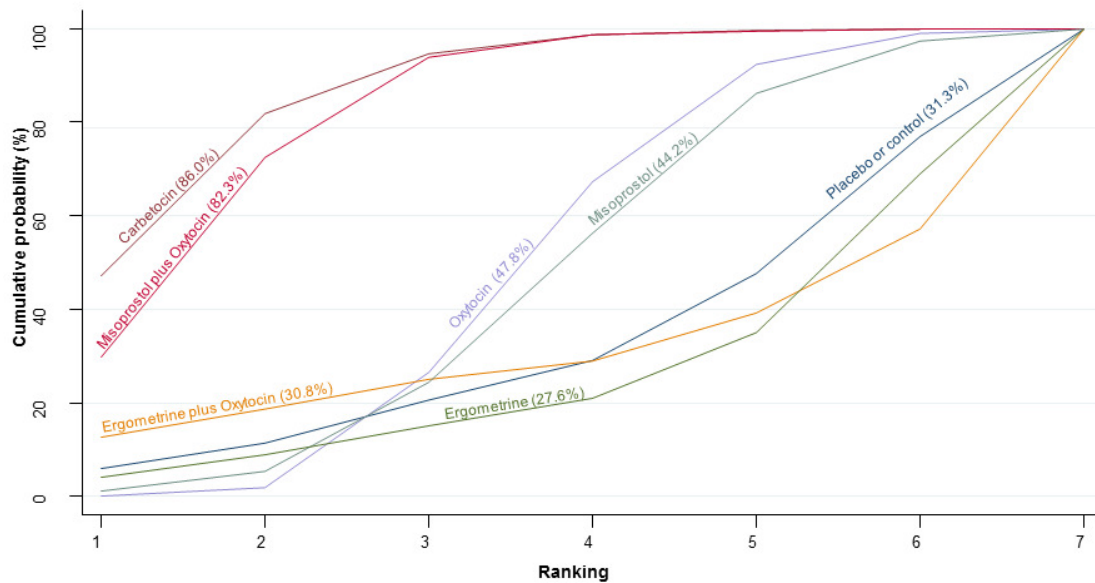
PPH ≥ 1000 mL

Pooled effect estimates from the network meta-analysis of 22 trials suggested a lack of evidence that any agent is worse or better than any other in preventing PPH ≥ 1000 mL in women at high risk for PPH; many of the comparisons were based on single studies (Appendix 3). There was no evidence of global inconsistency in this analysis (P = 0.851). Appendix 3 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 1000 mL for the subgroup including only trials with women at high risk for PPH. No clear ranking emerged in this analysis. Ergometrine and ergometrine plus oxytocin could not be ranked as there were no studies found comparing those with any other agents in the network.

Healthcare setting

Hospital setting

PPH ≥ 500 mL

The network diagram for PPH ≥ 500 mL for the subgroup including trials carried out in the hospital setting is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 95 trials suggested that all agents are effective for preventing PPH ≥ 500 mL when compared with placebo or no treatment (Figure 56). Ergometrine plus oxytocin, and misoprostol plus oxytocin were found to be more effective when compared with the standard agent oxytocin. Carbetocin also demonstrated a trend towards reduction of this outcome (Figure 56). Ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin were also found to be more effective when compared with misoprostol and ergometrine when used alone. There was evidence of global inconsistency in this analysis (P = 0.0448). However, we note that the CIs for both the network and direct evidence were overlapping across all comparisons suggesting locally-consistent results except for ergometrine versus placebo or no treatment based on a single study. Figure 57 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 500 mL for the subgroup including only trials carried out in the hospital setting. The highest ranked agents were ergometrine plus oxytocin, carbetocin, and misoprostol plus oxytocin with an almost 100% probability of these three agents being ranked first, second or third. Oxytocin was ranked fourth and its probability in being ranked in the top three agents was close to 0%.

Figure 56. **Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for prevention of PPH $\geq$ 500 mL by healthcare setting (hospital setting).**

		RR (95% CI)
Ergometrine vs Placebo or control (nma)		0.59 (0.42, 0.83)
(pairwise)		0.23 (0.10, 0.52)
Misoprostol vs Placebo or control (nma)		0.54 (0.41, 0.70)
(pairwise)		0.72 (0.43, 1.21)
Misoprostol plus Oxytocin vs Placebo or control (nma)		0.37 (0.26, 0.51)
(pairwise)		na
Carbetocin vs Placebo or control (nma)		0.37 (0.24, 0.55)
(pairwise)		0.75 (0.26, 2.15)
Ergometrine plus Oxytocin vs Placebo or control (nma)		0.35 (0.27, 0.46)
(pairwise)		0.36 (0.23, 0.57)
Oxytocin vs Placebo or control (nma)		0.50 (0.39, 0.65)
(pairwise)		0.51 (0.36, 0.72)
Ergometrine vs Oxytocin (nma)		1.17 (0.90, 1.53)
(pairwise)		1.30 (0.87, 1.94)
Misoprostol vs Oxytocin (nma)		1.07 (0.93, 1.22)
(pairwise)		1.07 (0.93, 1.24)
Misoprostol plus Oxytocin vs Oxytocin (nma)		0.73 (0.59, 0.90)
(pairwise)		0.73 (0.59, 0.90)
Carbetocin vs Oxytocin (nma)		0.73 (0.52, 1.01)
(pairwise)		0.71 (0.50, 1.02)
Ergometrine plus Oxytocin vs Oxytocin (nma)		0.70 (0.58, 0.84)
(pairwise)		0.72 (0.56, 0.92)
Ergometrine vs Ergometrine plus Oxytocin (nma)		1.67 (1.23, 2.28)
(pairwise)		0.16 (0.00, 4.25)
Misoprostol vs Ergometrine plus Oxytocin (nma)		1.52 (1.25, 1.86)
(pairwise)		1.75 (1.33, 2.31)
Misoprostol plus Oxytocin vs Ergometrine plus Oxytocin (nma)		1.04 (0.79, 1.37)
(pairwise)		1.41 (0.76, 2.61)
Carbetocin vs Ergometrine plus Oxytocin (nma)		1.04 (0.72, 1.49)
(pairwise)		0.96 (0.42, 2.18)
Ergometrine vs Carbetocin (nma)		1.60 (1.05, 2.44)
(pairwise)		na
Misoprostol vs Carbetocin (nma)		1.46 (1.03, 2.08)
(pairwise)		na
Misoprostol plus Oxytocin vs Carbetocin (nma)		1.00 (0.68, 1.48)
(pairwise)		
Ergometrine vs Misoprostol plus Oxytocin (nma)		1.59 (1.14, 2.23)
(pairwise)		na
Misoprostol vs Misoprostol plus Oxytocin (nma)		1.45 (1.14, 1.84)
(pairwise)		1.89 (1.10, 3.25)
Ergometrine vs Misoprostol (nma)		1.09 (0.84, 1.42)
(pairwise)		1.26 (0.91, 1.74)

Relative Risk (RR)

Figure 57. Cumulative rankograms comparing each of the uterotonic drugs for prevention of PPH ≥ 500 mL by healthcare setting (hospital setting).
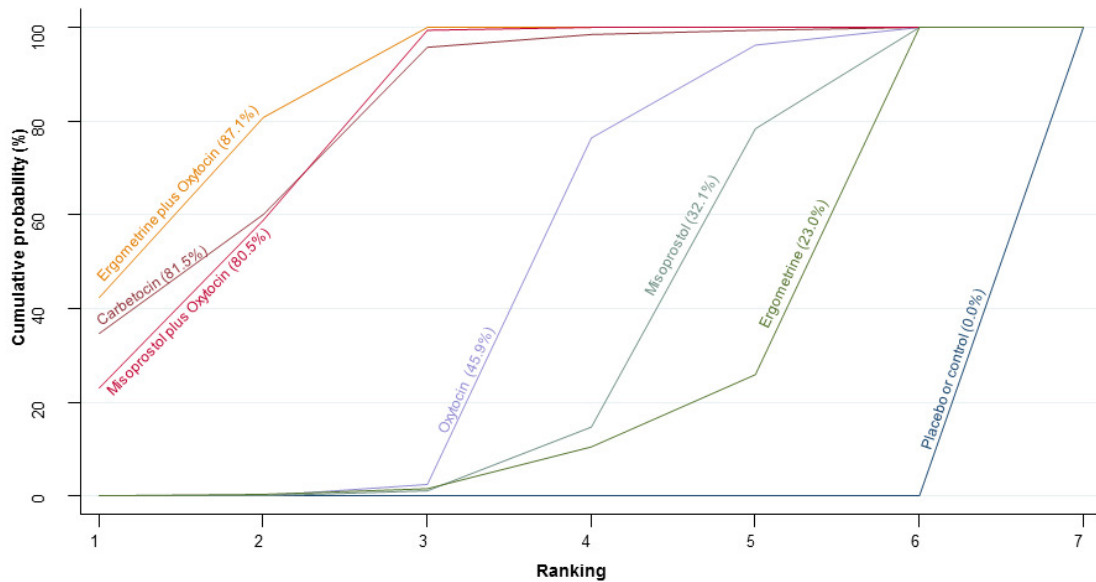
PPH ≥ 1000 mL

Pooled effect estimates from the network meta-analysis of 85 trials suggested that all agents except ergometrine are effective for preventing PPH ≥ 1000 mL when compared with placebo or no treatment for the subgroup including only trials carried out in the hospital setting (Appendix 3). Ergometrine plus oxytocin was the only agent found to be more effective when compared with the standard agent oxytocin. Carbetocin and misoprostol plus oxytocin demonstrated a trend towards reduction of this outcome (Appendix 3). There was no evidence of global inconsistency in this analysis (P = 0.389). Appendix 3 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 1000 mL for the subgroup including trials carried out in the hospital setting. The highest ranked agents were carbetocin, ergometrine plus oxytocin and misoprostol plus oxytocin. Oxytocin was still ranked fourth and its probability in being ranked in the top three agents was close to 20%.

Community setting

PPH ≥ 500 mL

Pooled effect estimates from the network meta-analysis of four trials suggested that only oxytocin and misoprostol are effective for preventing PPH ≥ 500 mL when compared with placebo or no treatment for the subgroup including only trials carried out in the community setting (Figure 58). There was evidence of global inconsistency in this analysis (P = 0.03), but most of the comparisons were based on a small number of studies. Figure 59 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 500 mL for the subgroup including trials carried out in the community setting. No clear ranking emerged in this analysis. Carbetocin, misoprostol plus oxytocin, ergometrine and ergometrine plus oxytocin could not be ranked as there were no studies found comparing those with any other agents in the network.

Figure 58. Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for prevention of PPH ≥ 500 mL by healthcare setting (community setting).
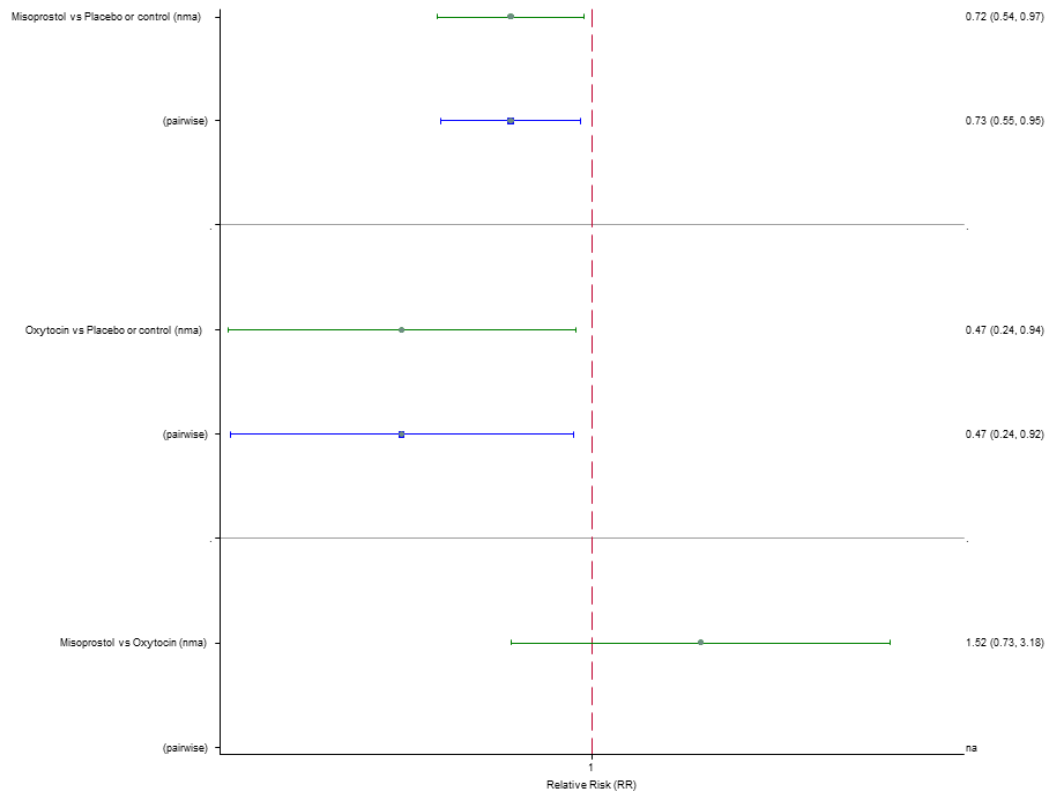
Figure 59.   Cumulative rankograms comparing each of the uterotonic drugs for prevention of PPH ≥ 500 mL by healthcare setting (community setting).
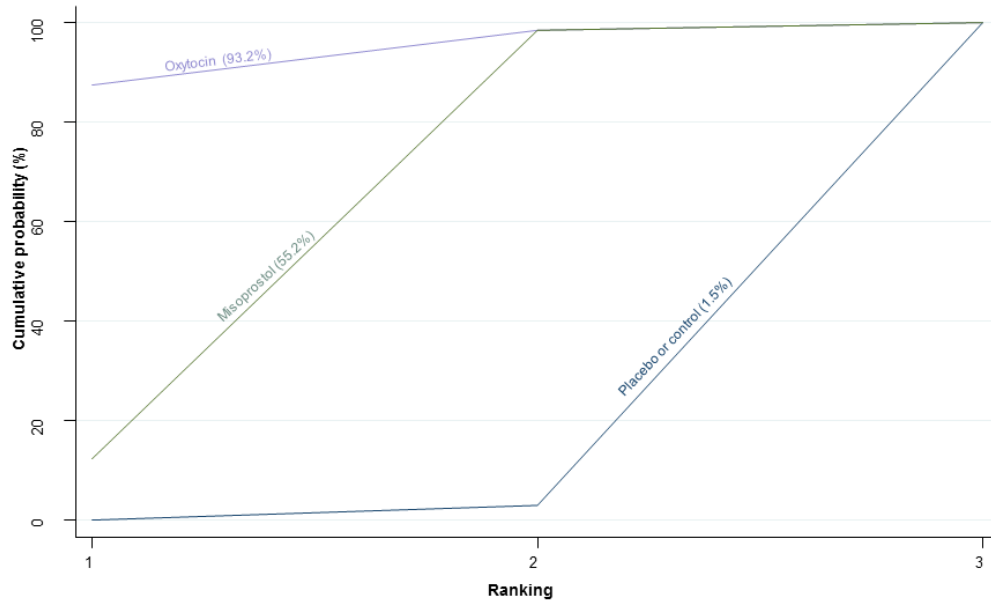
PPH ≥ 1000 mL

Pooled effect estimates from the network meta-analysis of four trials suggested that only misoprostol is more effective for preventing PPH ≥ 1000 mL when compared with placebo or no treatment. Oxytocin also demonstrated a trend towards reduction of this outcome for the subgroup including trials carried out in the community setting (Appendix 3). There was evidence of global inconsistency in this analysis (P = 0.004), but most of the comparisons were based on single studies. Appendix 3 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 1000 mL for the subgroup including trials carried out in the community setting. No clear ranking emerged in this analysis. Carbetocin, misoprostol plus oxytocin, ergometrine and ergometrine plus oxytocin could not be ranked as there were no studies found comparing those with any other agents in the network.

Intervention: dose, regimen or route

Low-dose misoprostol

PPH ≥ 500 mL

The network diagram for PPH ≥ 500 mL for the subgroup including only misoprostol studies that used a low dose (< 600 mcg) is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 72 trials suggested that all agents are effective for preventing PPH ≥ 500 mL when compared with placebo or no treatment (Figure 60). Ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin were found to be more effective when compared with the standard agent oxytocin (Figure 60). Ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin were also found to be more effective when compared with misoprostol and ergometrine when used alone. There was evidence of global inconsistency in this analysis (P = 0.016). However, we note that the CIs for both the network and direct evidence were overlapping across all comparisons suggesting locally-consistent

results except for ergometrine versus control or no treatment based on a single study. Figure 61 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 500 mL for the subgroup restricted to misoprostol trials that used a low dose. The highest ranked agents were ergometrine plus oxytocin, carbetocin, and misoprostol plus oxytocin with almost 100% probability of these three agents being ranked first, second or third. Oxytocin was ranked fourth and its probability in being ranked in the top three agents was close to 0%.

Figure 60. Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for prevention of PPH ≥ 500 mL restricted to misoprostol studies that use a low dose (less or equal to 500 mcg).
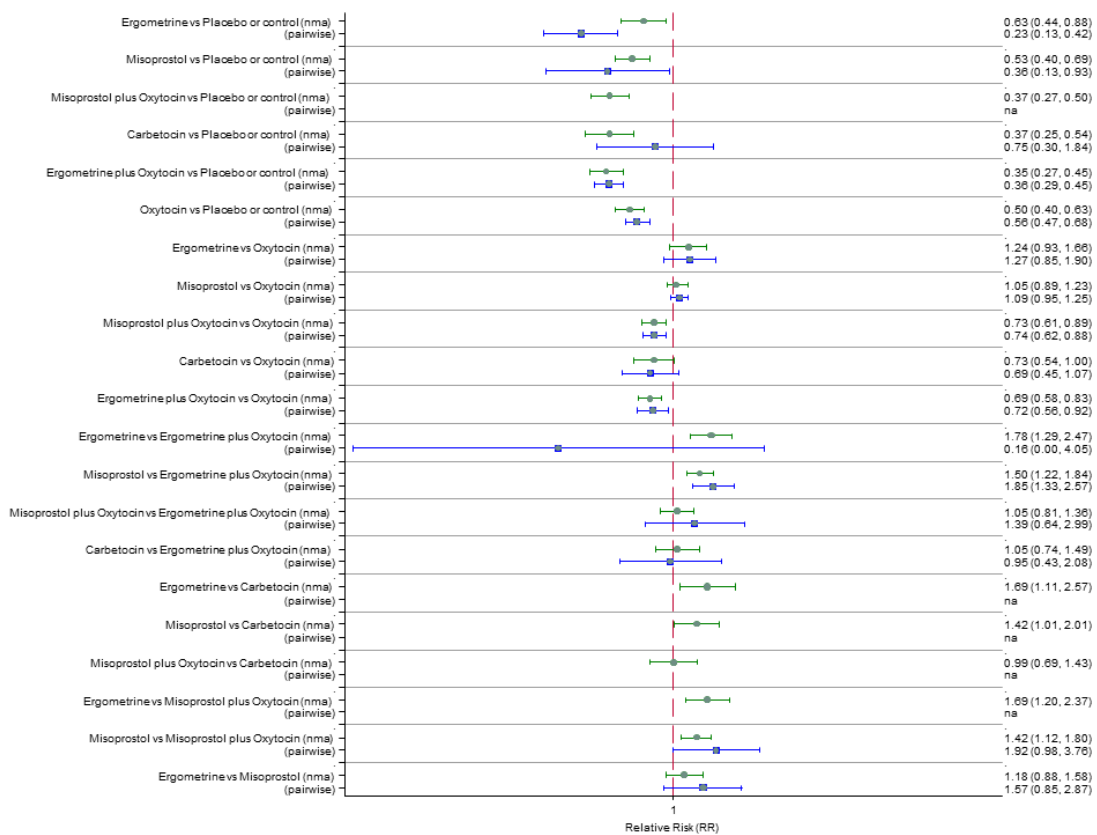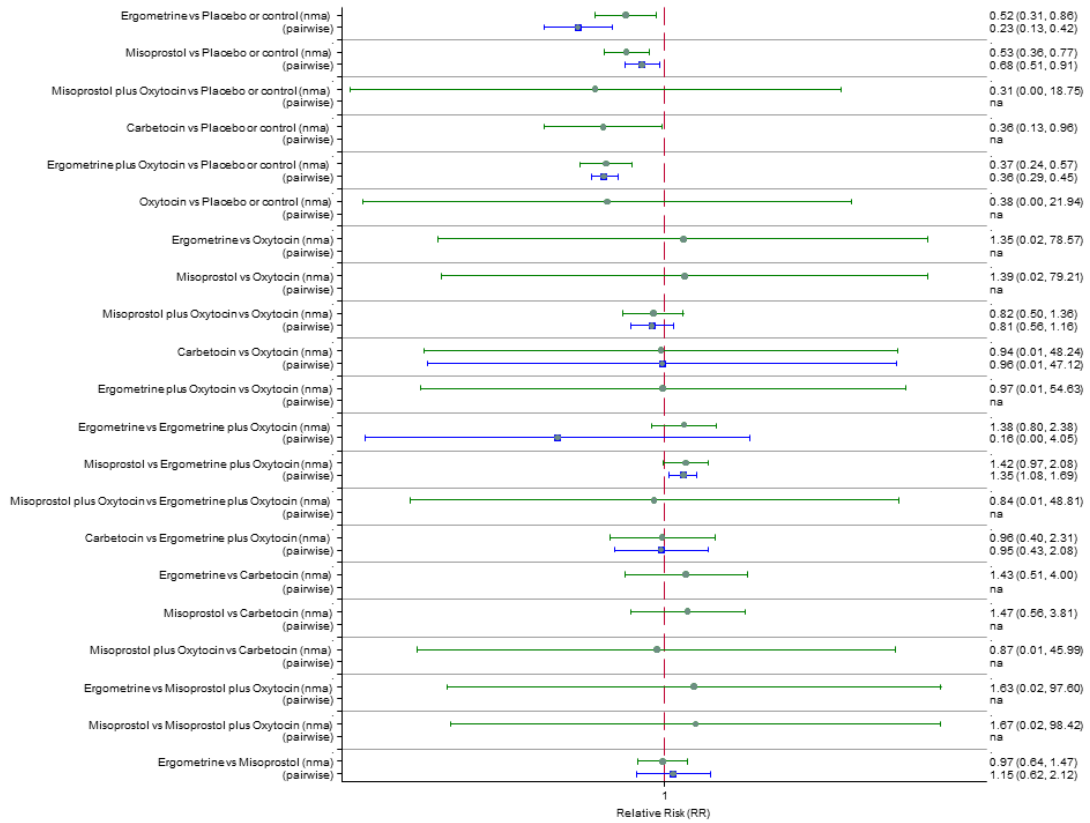
Figure 61. Cumulative rankograms comparing each of the uterotonic drugs for prevention of PPH ≥ 500 mL restricted to misoprostol studies that use a low dose (less or equal to 500 mcg).
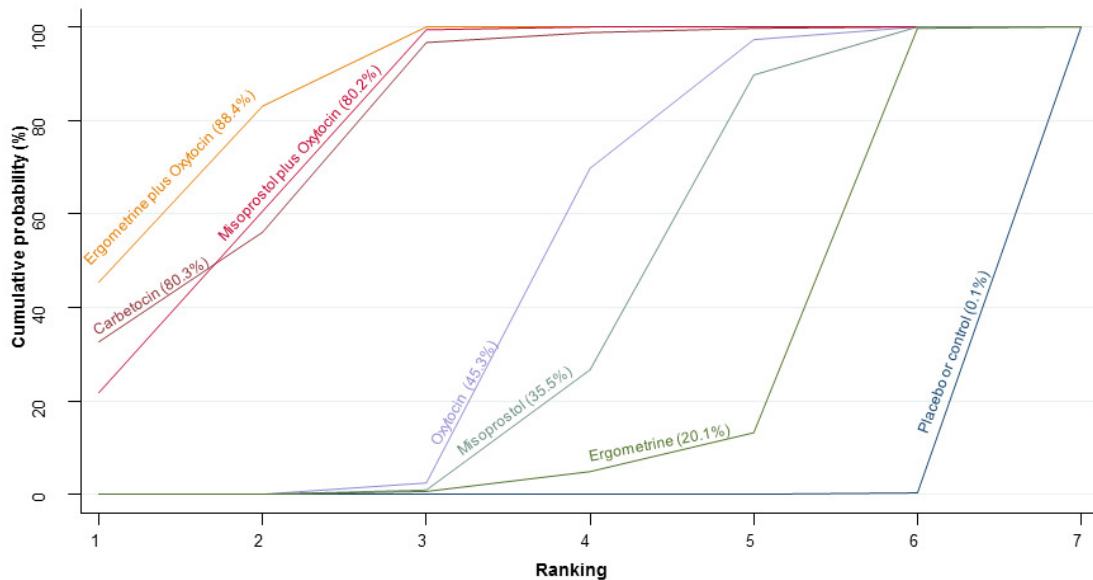
PPH ≥ 1000 mL

Pooled effect estimates from the network meta-analysis of 69 trials suggested that all agents except ergometrine are effective for preventing PPH ≥ 1000 mL when compared with placebo or no treatment for the subgroup including only misoprostol trials that used a low dose (Appendix 3). Ergometrine plus oxytocin was the only agent found to be more effective when compared with the standard agent oxytocin. Carbetocin also demonstrated a trend towards reduction of this outcome (Appendix 3). There was no evidence of global inconsistency in this analysis (P = 0.401). Appendix 3 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 1000 mL for the subgroup restricted to misoprostol trials that used a low dose. The highest ranked agents were carbetocin, ergometrine plus oxytocin and misoprostol plus oxytocin. Oxytocin was still ranked fourth and its probability in being ranked in the top three agents was close to 20%.

High-dose misoprostol

PPH ≥ 500 mL

The network diagram for PPH ≥ 500 mL for the subgroup including only misoprostol studies that used a high dose (≥ 600 mcg) is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 83 trials suggested that all agents are effective for preventing PPH ≥ 500 mL when compared with placebo or no treatment for the subgroup including only misoprostol trials that used a high dose (Figure 62). Ergometrine plus oxytocin and misoprostol plus oxytocin were found to be more effective when compared with the standard agent oxytocin. Carbetocin also showed a trend towards reduction of this outcome (Figure 62). Ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin were also found to be more effective than misoprostol when used alone. There was no evidence of global inconsistency in this analysis (P = 0.322). Figure 63 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 500 mL for the subgroup including only misoprostol trials that used a high dose. The highest ranked agents were ergometrine plus oxytocin, carbetocin, and misoprostol plus oxytocin with more than 80% probability of these three agents being ranked first, second or third. Oxytocin was ranked fifth behind ergometrine and its probability in being ranked in the top three agents was close to 0%.

Figure 62. Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for prevention of PPH ≥ 500 mL restricted to misoprostol studies that use a high dose (600 mcg or more).

Ergometrine vs Placebo or control (nma)	0.50 (0.35, 0.71)
(pairwise)	0.23 (0.13, 0.42)
Misoprostol vs Placebo or control (nma)	0.64 (0.51, 0.80)
(pairwise)	0.77 (0.62, 0.97)
Misoprostol plus Oxytocin vs Placebo or control (nma)	0.43 (0.31, 0.58)
(pairwise)	na
Carbetocin vs Placebo or control (nma)	0.42 (0.28, 0.61)
(pairwise)	0.75 (0.30, 1.84)
Ergometrine plus Oxytocin vs Placebo or control (nma)	0.42 (0.32, 0.55)
(pairwise)	0.36 (0.29, 0.45)
Oxytocin vs Placebo or control (nma)	0.57 (0.46, 0.70)
(pairwise)	0.56 (0.49, 0.65)
Ergometrine vs Oxytocin (nma)	0.87 (0.62, 1.22)
(pairwise)	1.13 (0.57, 2.25)
Misoprostol vs Oxytocin (nma)	1.12 (0.92, 1.35)
(pairwise)	1.07 (0.77, 1.49)
Misoprostol plus Oxytocin vs Oxytocin (nma)	0.74 (0.59, 0.93)
(pairwise)	0.75 (0.62, 0.90)
Carbetocin vs Oxytocin (nma)	0.73 (0.52, 1.01)
(pairwise)	0.69 (0.45, 1.07)
Ergometrine plus Oxytocin vs Oxytocin (nma)	0.74 (0.59, 0.92)
(pairwise)	0.80 (0.67, 0.95)
Ergometrine vs Ergometrine plus Oxytocin (nma)	1.17 (0.79, 1.73)
(pairwise)	0.16 (0.00, 4.05)
Misoprostol vs Ergometrine plus Oxytocin (nma)	1.51 (1.16, 1.97)
(pairwise)	1.39 (0.96, 2.02)
Misoprostol plus Oxytocin vs Ergometrine plus Oxytocin (nma)	1.00 (0.73, 1.38)
(pairwise)	na
Carbetocin vs Ergometrine plus Oxytocin (nma)	0.98 (0.67, 1.43)
(pairwise)	0.95 (0.43, 2.08)
Ergometrine vs Carbetocin (nma)	1.19 (0.75, 1.90)
(pairwise)	na
Misoprostol vs Carbetocin (nma)	1.53 (1.05, 2.22)
(pairwise)	na
Misoprostol plus Oxytocin vs Carbetocin (nma)	1.02 (0.68, 1.52)
(pairwise)	na
Ergometrine vs Misoprostol plus Oxytocin (nma)	1.16 (0.78, 1.75)
(pairwise)	na
Misoprostol vs Misoprostol plus Oxytocin (nma)	1.50 (1.11, 2.01)
(pairwise)	na
Ergometrine vs Misoprostol (nma)	0.77 (0.55, 1.08)
(pairwise)	0.87 (0.64, 1.17)

Relative Risk (RR)

Figure 63. Cumulative rankograms comparing each of the uterotonic drugs for prevention of PPH ≥ 1000 mL restricted to misoprostol studies that use a high dose (600 mcg or more).
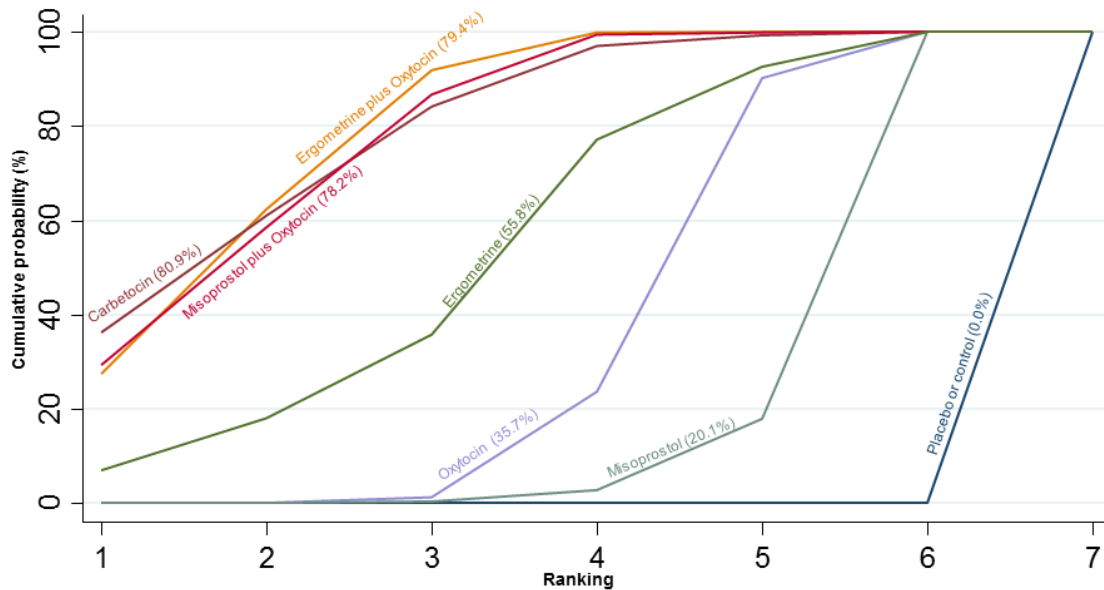
PPH ≥ 1000 mL

Pooled effect estimates from the network meta-analysis of 62 trials suggested that all agents except ergometrine are effective for preventing PPH ≥ 1000 mL when compared with placebo or no treatment for the subgroup including only misoprostol trials that used a high dose (Appendix 3). Ergometrine plus oxytocin was the only agent found to be more effective when compared with the standard agent oxytocin. Carbetocin also demonstrated a trend towards reduction of this outcome (Appendix 3). Ergometrine plus oxytocin, carbetocin, misoprostol plus oxytocin and oxytocin when used alone were found to be more effective than misoprostol despite misoprostol being used at a high dose. There was no evidence of global inconsistency in this analysis (P = 0.625). Appendix 3 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 1000 mL for the subgroup restricted to misoprostol trials that used a high dose. The highest ranked agents were carbetocin, ergometrine plus oxytocin, ergometrine and misoprostol plus oxytocin. Oxytocin was still ranked fifth and its probability in being ranked in the top three agents was less than 20%.

Oxytocin bolus only

PPH ≥ 500 mL

The network diagram for PPH ≥ 500 mL for the subgroup is presented in Appendix 2. This subgroup includes all trials, but for trials including oxytocin as an arm, this analysis is restricted to oxytocin studies that used an intravenous or intramuscular bolus of any dose and excluded studies that used a bolus plus infusion or infusion only of oxytocin. Pooled effect estimates from the network meta-analysis of 84 trials suggested that all agents are effective for preventing PPH ≥ 500 mL when compared with placebo or no treatment for the subgroup including trials that only used an intramuscular or intravenous bolus of oxytocin at any dose (Figure 64). Ergometrine plus oxytocin was the only agent found to be more effective when compared with the standard agent oxytocin. Carbetocin and misoprostol plus oxytocin also demonstrated a trend towards reduction of this outcome (Figure 64). Ergometrine plus oxytocin was also found to be more effective than misoprostol when used alone. There was no evidence of global inconsistency in this analysis (P = 0.134). Figure 65 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 500 mL for the subgroup including trials that used an intramuscular or intravenous bolus of oxytocin at any dose. The highest ranked agents were ergometrine plus oxytocin, misoprostol plus oxytocin and carbetocin with more than 80% probability of these three agents being ranked first, second or third. Oxytocin was still ranked fourth and its probability in being ranked in the top three agents was less than 20%.

Figure 64. Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for prevention of PPH $\geq$ 500 mL restricted to oxytocin studies that used an intramuscular or intravenous bolus of any dose.
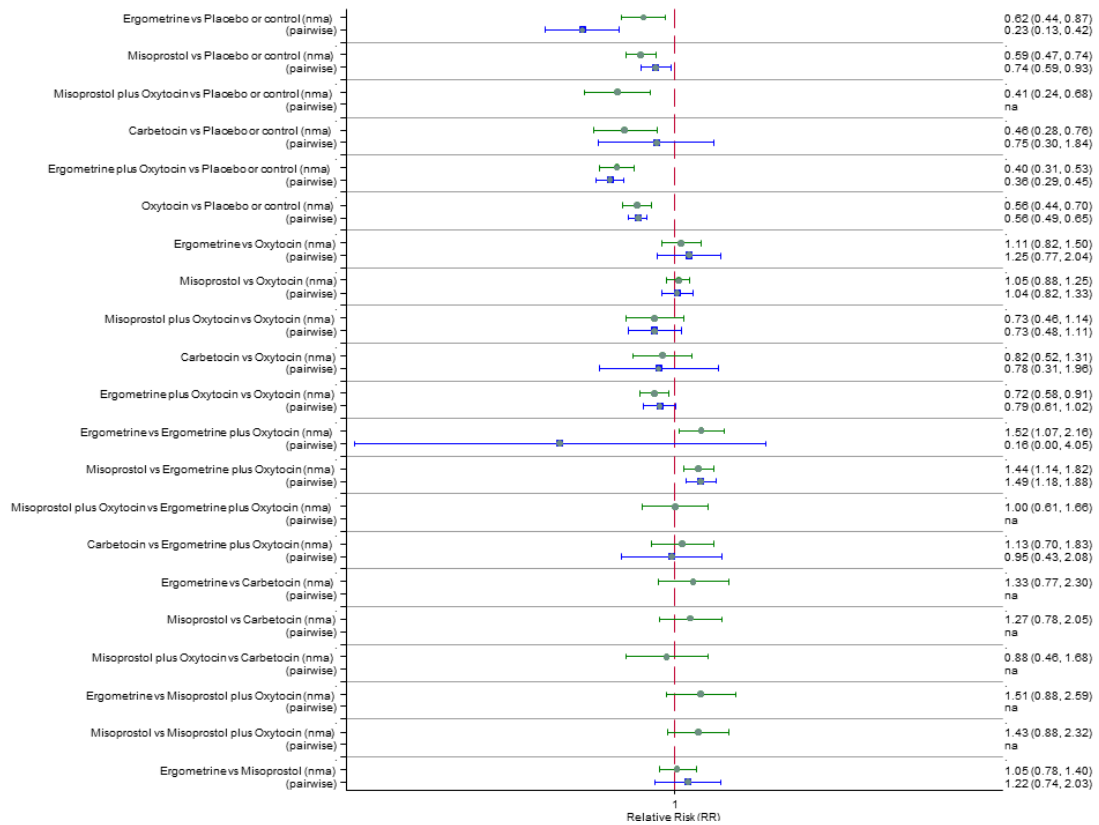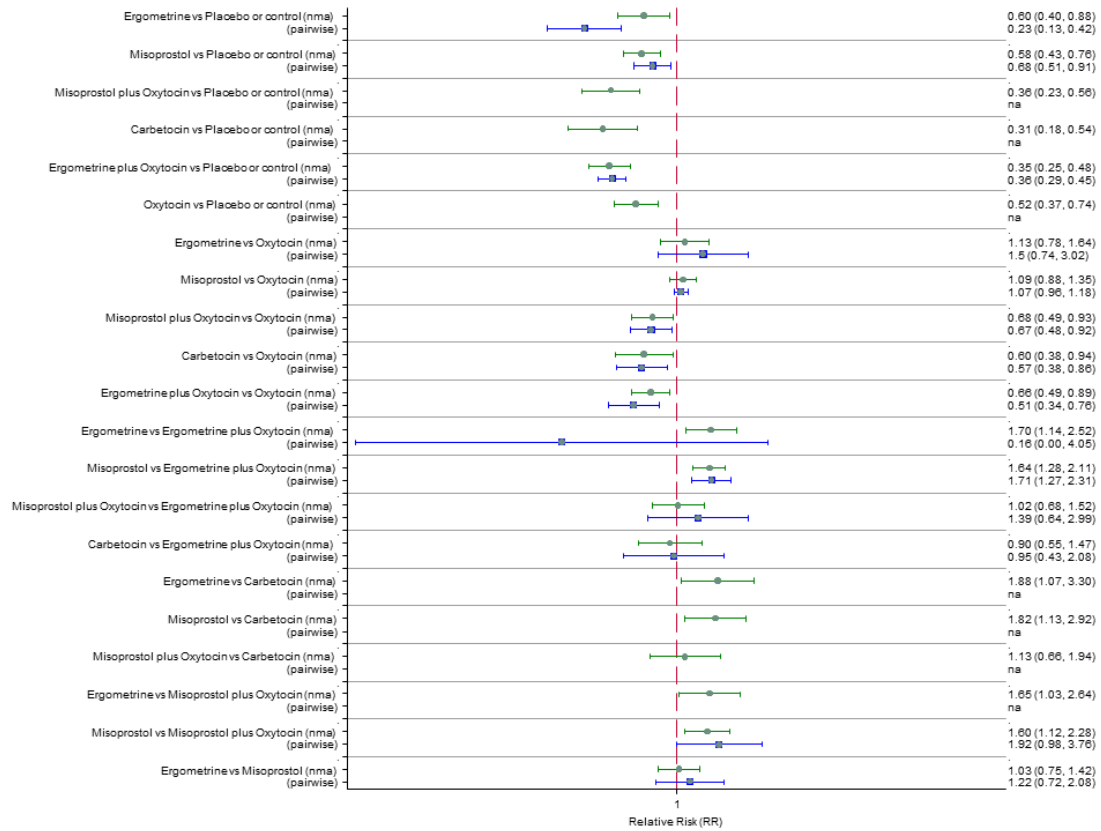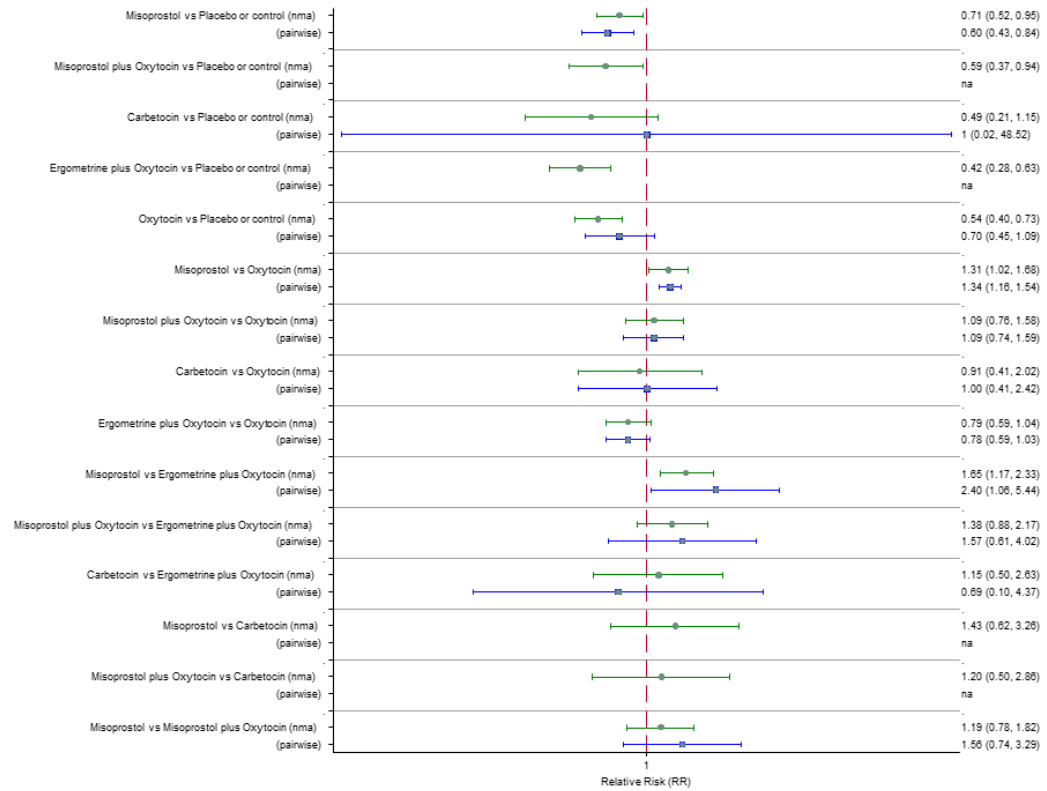
Figure 65. Cumulative rankograms comparing each of the uterotonic drugs for prevention of PPH ≥ 500 mL restricted to oxytocin studies that used an intramuscular or intravenous bolus of any dose.
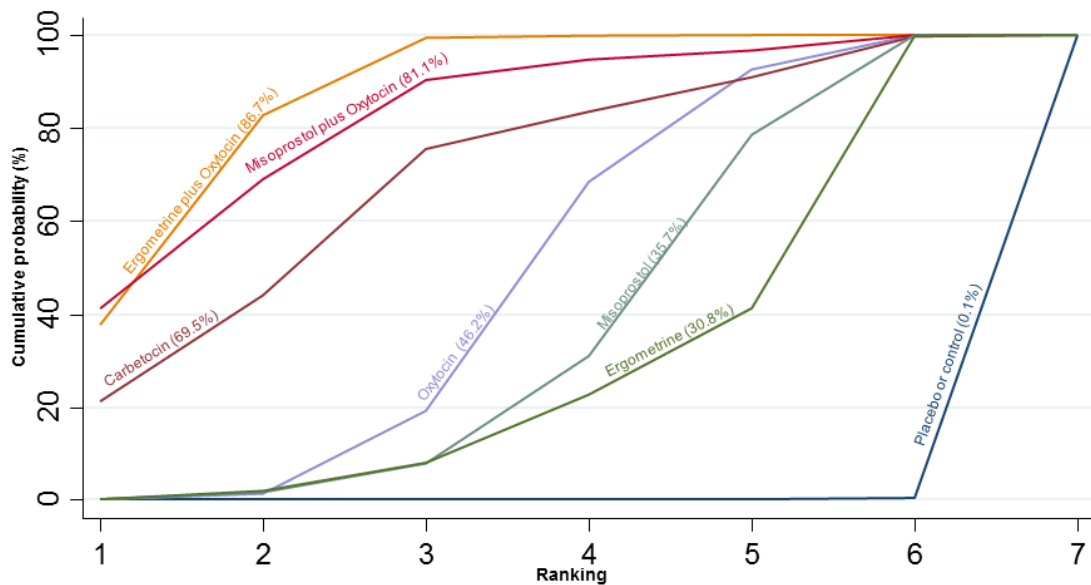
PPH ≥ 1000 mL

The network diagram for PPH ≥ 1000 mL for the subgroup including all trials, but restricted to trials that used an intravenous or intramuscular bolus of oxytocin at any dose is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 68 trials suggested that all agents except carbetocin and ergometrine are effective for preventing PPH ≥ 500 mL when compared with placebo or no treatment for the subgroup including only trials that used an intramuscular or intravenous bolus of oxytocin at any dose (Appendix 3). None of the agents was found to be more effective when compared with the standard agent oxytocin (Appendix 3). Ergometrine plus oxytocin and oxytocin when used alone were found to be more effective than misoprostol. There was no evidence of global inconsistency in this analysis (P = 0.468). Appendix 3 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 1000 mL for the subgroup restricted to oxytocin studies that used an intramuscular or intravenous bolus of any dose. The highest ranked agent was ergometrine plus oxytocin with less clear ranking amongst the other agents.

Oxytocin bolus plus infusion

PPH ≥ 500 mL

The network diagram for PPH ≥ 500 mL for this subgroup is presented in Appendix 2. This subgroup includes all trials, but when oxytocin was used as an arm in the trial this analysis is restricted only to studies that used an intravenous bolus with an intravenous infusion of oxytocin at any dose and excluded studies that used an intravenous or intramuscular bolus or an intravenous infusion only of oxytocin. Pooled effect estimates from the network meta-analysis of 31 trials suggested that all agents except oxytocin and misoprostol plus oxytocin are effective for preventing PPH ≥ 500 mL when compared with placebo or no treatment for the subgroup including oxytocin trials that used an intravenous bolus plus an infusion of any dose (Figure 66). The active agents were comparable between them, but most of the comparisons were underpowered to detect a difference. There was no evidence of global inconsistency in this analysis (P = 0.081). Figure 67 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 500 mL for the subgroup including only trials of oxytocin that used an intravenous bolus plus an infusion of any dose. No clear ranking emerged in this analysis.

Figure 66. Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for prevention of PPH ≥ 500 mL restricted to oxytocin studies that used an intravenous bolus plus an infusion of any dose.
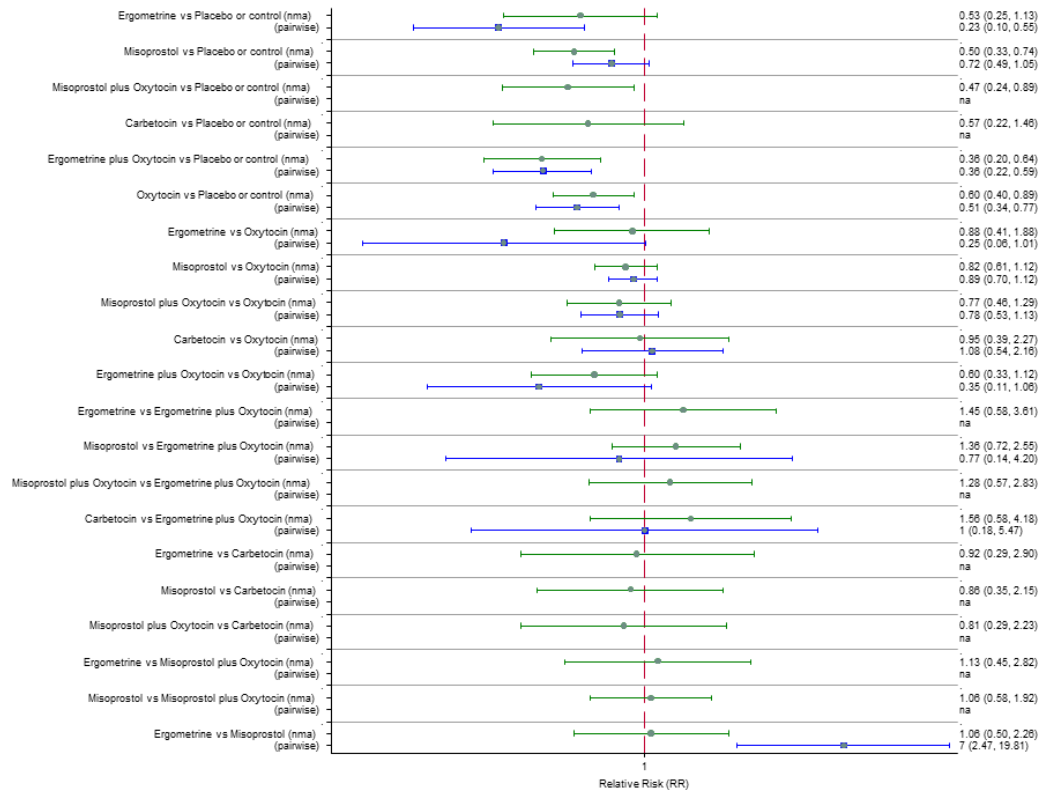
Figure 67. Cumulative rankograms comparing each of the uterotonic drugs for prevention of PPH ≥ 500 mL restricted to oxytocin studies that used an intravenous bolus plus an infusion of any dose.
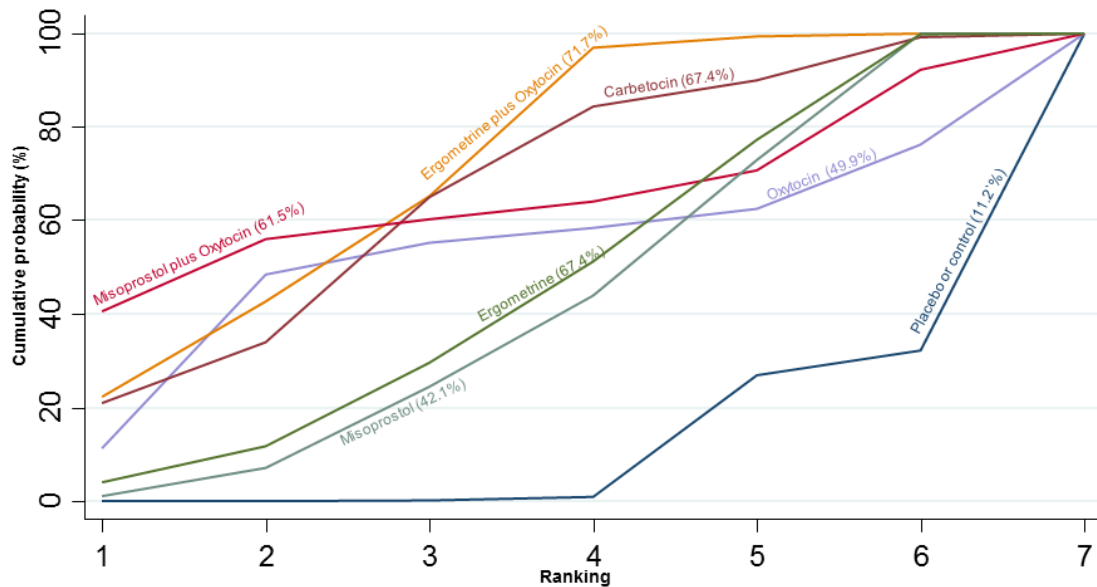
PPH ≥ 1000 mL

The network diagram for PPH ≥ 1000 mL for this subgroup is presented in Appendix 2. This subgroup includes all trials, but it is restricted to studies that used an intravenous bolus with an intravenous infusion of oxytocin at any dose. Pooled effect estimates from the network meta-analysis of 29 trials suggested that all agents demonstrated a similar trend for reducing occurrence of this outcome, but only ergometrine, misoprostol and ergometrine plus oxytocin reached statistical significance when compared with placebo or no treatment for this subgroup (Appendix 3). The active agents were comparable between them, but most of the comparisons were underpowered to detect a difference. There was no evidence of global inconsistency in this analysis (P = 0.315). Appendix 3 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 1000 mL for the subgroup including oxytocin studies that used an intravenous bolus plus an infusion of any dose. No clear ranking emerged in this analysis.

Oxytocin infusion only

PPH ≥ 500 mL

The network diagram for PPH ≥ 500 mL for this subgroup is presented in Appendix 2. This subgroup includes all trials, but when oxytocin was used as an arm in the trial this analysis is restricted to studies that used an intravenous infusion only of oxytocin at any dose and excluded studies that used an intravenous or intramuscular bolus or an intravenous bolus plus an intravenous infusion of oxytocin. Pooled effect estimates from the network meta-analysis of 48 trials suggested that all agents are effective for preventing PPH ≥ 500 mL when compared with placebo or no treatment for the subgroup including oxytocin trials that used an intravenous infusion only of any dose (Figure 68). The active agents were comparable between them, but most of the comparisons were underpowered to detect a difference. There was no evidence of global inconsistency in this analysis (P = 0.135). Figure 69 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 500 mL for the subgroup including oxytocin trials that used an intravenous infusion only of any dose. The highest ranked agents were carbetocin, ergometrine plus oxytocin and misoprostol plus oxytocin with almost 100% probability of these three agents being ranked first, second or third. Oxytocin was ranked fourth and its probability in being ranked in the top three agents was almost 0%.

Figure 68.   Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for prevention of PPH $\geq$ 500 mL restricted to oxytocin studies that used an intravenous infusion only of any dose.
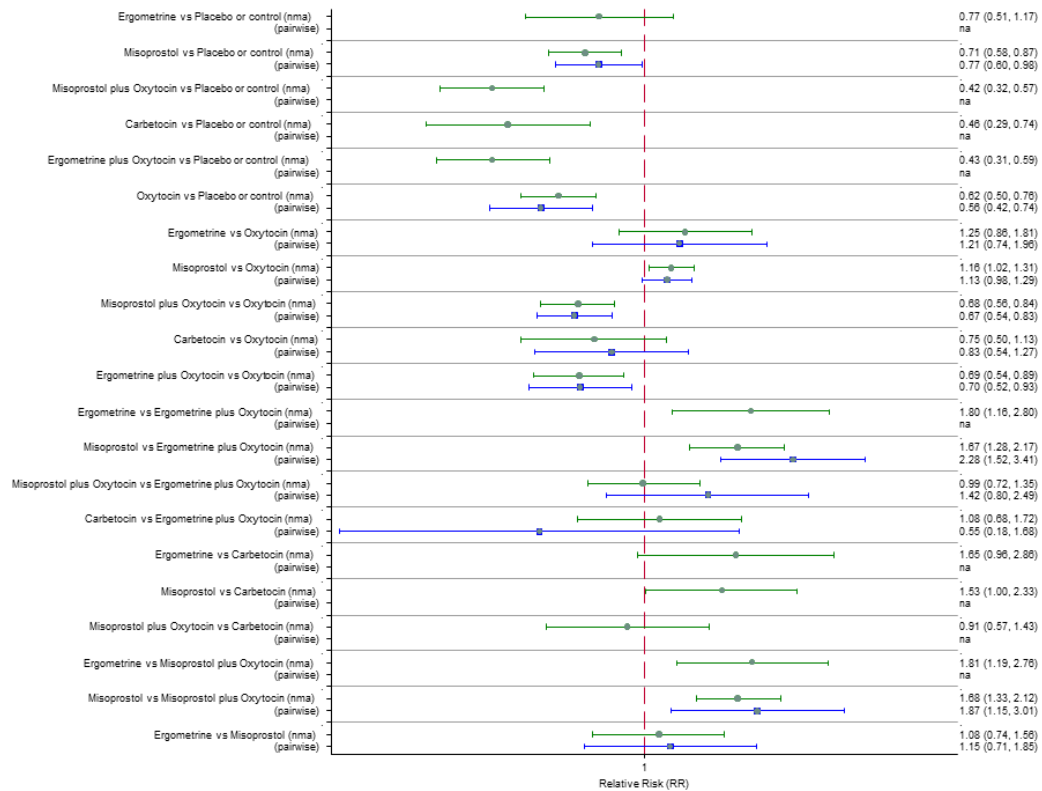
Figure 69. Cumulative rankograms comparing each of the uterotonic drugs for prevention of PPH ≥ 500 mL restricted to oxytocin studies that used an intravenous infusion only of any dose.
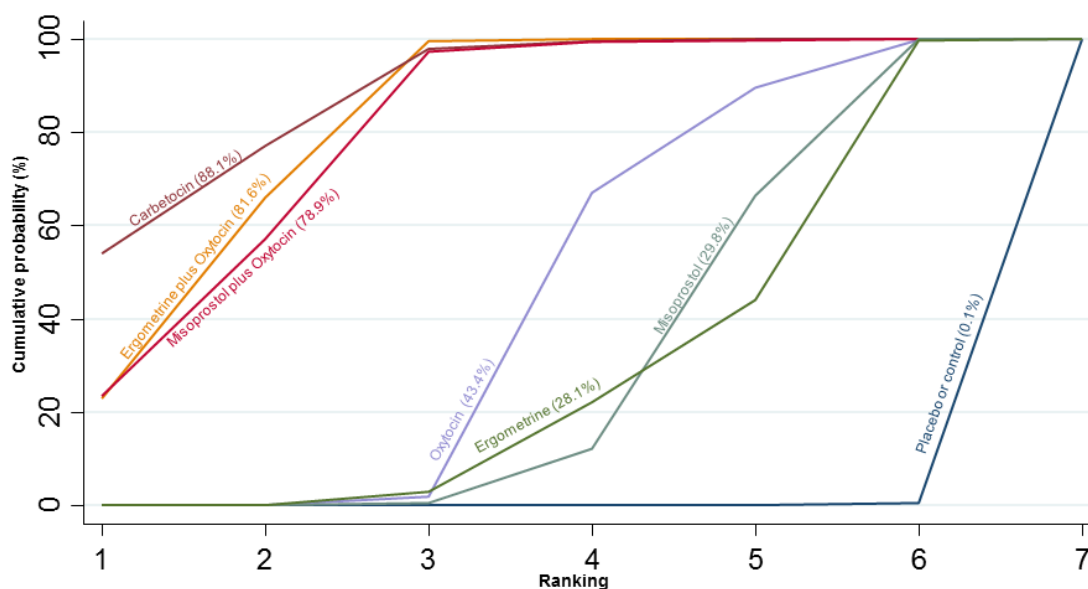
PPH ≥ 1000 mL

The network diagram for PPH ≥ 1000 mL for the subgroup including all trials, but restricted to oxytocin trials that used an intravenous infusion only of any dose is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 41 trials suggested that all agents except oxytocin and ergometrine are effective for preventing PPH ≥ 500 mL when compared with placebo or no treatment for the subgroup including only oxytocin trials that used an intravenous infusion only of any dose (Appendix 3). Ergometrine plus oxytocin and carbetocin were found to be more effective when compared with the standard agent oxytocin (Appendix 3). Ergometrine plus oxytocin and carbetocin were also found to be more effective than misoprostol. There was no evidence of global inconsistency in this analysis (P = 0.232). Appendix 3 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 1000 mL for the subgroup including oxytocin studies that used an intravenous infusion only of any dose. The highest ranked agent was carbetocin. There is less clear ranking for the rest of the agents but on this analysis oxytocin was ranked sixth lower than ergometrine and misoprostol with 0% probability of being ranked in the top three.

Sensitivity analyses

Low risk of bias studies

PPH ≥ 500 mL

The network diagram for PPH ≥ 500 mL for low risk of bias trials (double-blinded, adequately concealed with less than 10% loss to follow-up) is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 29 low risk of bias trials suggested that all agents except carbetocin are effective for preventing PPH ≥ 500 mL when compared with placebo or no treatment. Carbetocin demonstrated a similar trend towards reduction of this outcome (Figure 70). Ergometrine plus oxytocin, and ergometrine were found to be more effective when compared with the standard agent oxytocin (Figure 70). Ergometrine plus oxytocin and ergometrine were also found to be more effective when compared with misoprostol when used alone. There was no evidence of global inconsistency in this analysis (P = 0.844). Figure 71 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 500 mL for the low risk of bias trials. The highest ranked agents were ergometrine, ergometrine plus oxytocin and misoprostol plus oxytocin. Oxytocin was ranked fourth and its probability in being ranked in the top three agents was less than 10%. Carbetocin dropped its ranking from second in the global analysis for PPH ≥ 500 mL to fifth behind oxytocin in this analysis including only low risk of bias trials. The ranking

of ergometrine is an extreme outlier in this analysis and is based
on a single study.

Figure 70.   Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for prevention of PPH $\geq$ 500 mL restricted to low risk of bias studies only.

Misoprostol vs Placebo or control (nma)	0.71 (0.52, 0.95)
(pairwise)	0.60 (0.43, 0.84)
Misoprostol plus Oxytocin vs Placebo or control (nma)	0.59 (0.37, 0.94)
(pairwise)	na
Carbetocin vs Placebo or control (nma)	0.49 (0.21, 1.15)
(pairwise)	1 (0.02, 48.52)
Ergometrine plus Oxytocin vs Placebo or control (nma)	0.42 (0.28, 0.63)
(pairwise)	na
Oxytocin vs Placebo or control (nma)	0.54 (0.40, 0.73)
(pairwise)	0.70 (0.45, 1.09)
Misoprostol vs Oxytocin (nma)	1.31 (1.02, 1.68)
(pairwise)	1.34 (1.16, 1.54)
Misoprostol plus Oxytocin vs Oxytocin (nma)	1.09 (0.76, 1.58)
(pairwise)	1.09 (0.74, 1.59)
Carbetocin vs Oxytocin (nma)	0.91 (0.41, 2.02)
(pairwise)	1.00 (0.41, 2.42)
Ergometrine plus Oxytocin vs Oxytocin (nma)	0.79 (0.59, 1.04)
(pairwise)	0.78 (0.59, 1.03)
Misoprostol vs Ergometrine plus Oxytocin (nma)	1.65 (1.17, 2.33)
(pairwise)	2.40 (1.06, 5.44)
Misoprostol plus Oxytocin vs Ergometrine plus Oxytocin (nma)	1.38 (0.88, 2.17)
(pairwise)	1.57 (0.61, 4.02)
Carbetocin vs Ergometrine plus Oxytocin (nma)	1.15 (0.50, 2.63)
(pairwise)	0.69 (0.10, 4.37)
Misoprostol vs Carbetocin (nma)	1.43 (0.62, 3.26)
(pairwise)	na
Misoprostol plus Oxytocin vs Carbetocin (nma)	1.20 (0.50, 2.86)
(pairwise)	na
Misoprostol vs Misoprostol plus Oxytocin (nma)	1.19 (0.78, 1.82)
(pairwise)	1.56 (0.74, 3.29)

1
Relative Risk (RR)

Figure 71. Cumulative rankograms comparing each of the uterotonic drugs for prevention of PPH ≥ 500 mL restricted to low risk of bias studies only.
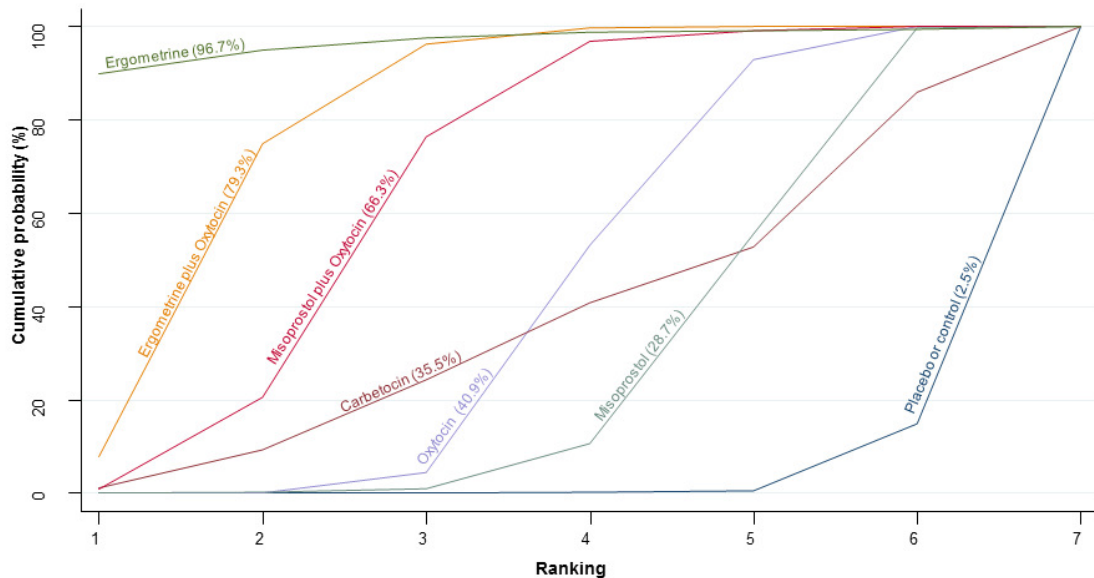
PPH ≥ 1000 mL

The network diagram for PPH ≥ 1000 mL for low risk of bias trials is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 30 high-quality trials suggested that all agents except carbetocin are effective for preventing PPH ≥ 1000 mL when compared with placebo or no treatment. Carbetocin demonstrated a similar trend towards reduction of this outcome (Appendix 3). Oxytocin was found to be better than misoprostol when used alone (Appendix 3). Ergometrine plus oxytocin was also found to be more effective when compared with misoprostol when used alone. There was no evidence of global inconsistency in this analysis (P = 0.802). Appendix 3 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 1000 mL for the low risk of bias trials. The highest ranked agent was ergometrine plus oxytocin. The ranking for carbetocin, oxytocin and misoprostol plus oxytocin was very close without a clear hierarchy.

Studies with funding source at low risk of bias (public or no funding)

PPH ≥ 500 mL

The network diagram for PPH ≥ 500 mL for studies with public or no funding is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 32 trials suggested that all agents except carbetocin and ergometrine are effective for preventing PPH ≥ 500 mL when compared with placebo or no treatment. All other agents demonstrated a similar trend towards reduction of this outcome (Figure 72). There were no significant differences between the active agents. There was evidence of global inconsistency in this analysis (P = 0.0003). However, we note that the CIs for both the network and direct evidence were overlapping across all comparisons suggesting locally-consistent results except for ergometrine versus misoprostol based on a single study. Figure 73 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 500 mL for trials with public or no funding. The highest ranked agent was ergometrine plus oxytocin. The ranking for carbetocin, oxytocin and misoprostol plus oxytocin was very close without a clear hierarchy.

**Figure 72. Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for prevention of PPH ≥ 500 mL restricted to studies with funding source at low risk of bias (public or no funding).**

Figure 73. Cumulative rankograms comparing each of the uterotonic drugs for prevention of PPH ≥ 500 mL restricted to studies with funding source at low risk of bias (public or no funding).
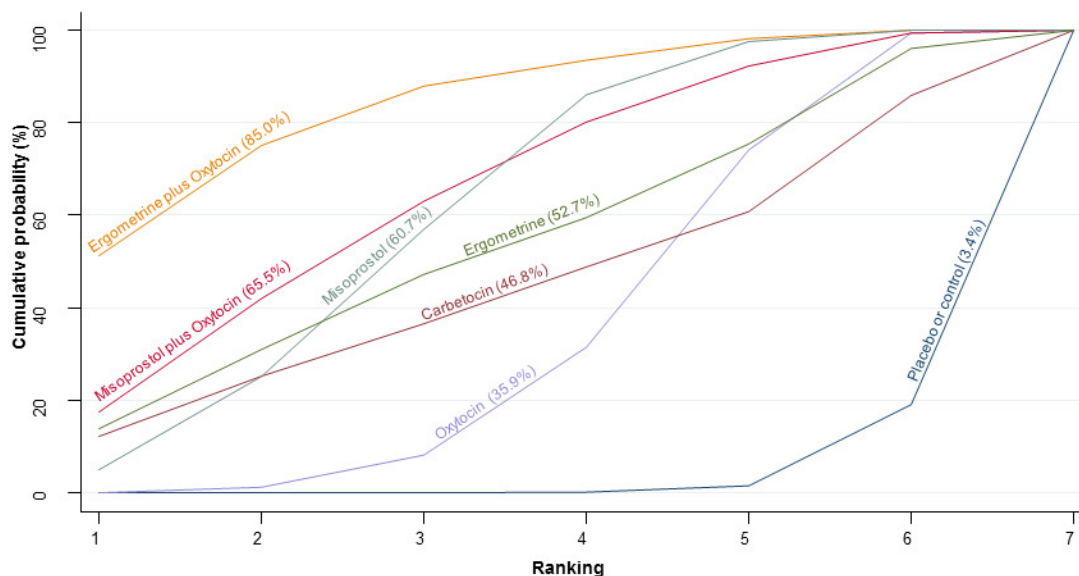
PPH ≥ 1000 mL

The network diagram for PPH ≥ 1000 mL for trials with public or no funding is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 35 trials suggested that all agents except carbetocin are effective for preventing PPH ≥ 1000 mL when compared with placebo or no treatment. Carbetocin demonstrated a similar trend towards reduction of this outcome (Appendix 3). No agent was found to be significantly better or worse than oxytocin (Appendix 3). Ergometrine was found to be more effective when compared with misoprostol. There was no evidence of global inconsistency in this analysis (P = 0.739). Appendix 3 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 1000 mL for the trials with public or no funding. The highest ranked agents were ergometrine and ergometrine plus oxytocin. The ranking for carbetocin, oxytocin and misoprostol plus oxytocin was very close without a clear hierarchy. The ranking of ergometrine was an outlier in this analysis and was based on a single study.

Studies with an objective method of measuring blood loss

PPH ≥ 500 mL

The network diagram for PPH ≥ 500 mL for the trials that used an objective method for measuring blood loss is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 56 trials suggested that all agents except ergometrine are effective for preventing PPH ≥ 500 mL when compared with placebo or no treatment (Figure 74). Ergometrine plus oxytocin and misoprostol plus oxytocin were found to be more effective when compared with the standard agent oxytocin with carbetocin also demonstrating a similar trend (Figure 74). Ergometrine plus oxytocin and misoprostol plus oxytocin were also found to be more effective than misoprostol and ergometrine when used alone. There was no evidence of global inconsistency in this analysis (P = 0.455). Figure 75 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 500 mL for trials that used an objective method of measuring blood loss. The highest ranked agents were ergometrine plus oxytocin and misoprostol plus oxytocin followed closely by carbetocin with almost 100% probability of these three agents being ranked first, second or third. Oxytocin was ranked fourth and its probability in being ranked in the top three agents was less than 0%.

Figure 74. Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for prevention of PPH ≥ 500 mL restricted to studies with an objective method of measuring blood loss.

	RR (95% CI)
Ergometrine vs Placebo or control (nma)	0.77 (0.51, 1.17)
(pairwise)	na
Misoprostol vs Placebo or control (nma)	0.71 (0.58, 0.87)
(pairwise)	0.77 (0.60, 0.98)
Misoprostol plus Oxytocin vs Placebo or control (nma)	0.42 (0.32, 0.57)
(pairwise)	na
Carbetocin vs Placebo or control (nma)	0.46 (0.29, 0.74)
(pairwise)	na
Ergometrine plus Oxytocin vs Placebo or control (nma)	0.43 (0.31, 0.59)
(pairwise)	na
Oxytocin vs Placebo or control (nma)	0.62 (0.50, 0.76)
(pairwise)	0.56 (0.42, 0.74)
Ergometrine vs Oxytocin (nma)	1.25 (0.86, 1.81)
(pairwise)	1.21 (0.74, 1.96)
Misoprostol vs Oxytocin (nma)	1.16 (1.02, 1.31)
(pairwise)	1.13 (0.98, 1.29)
Misoprostol plus Oxytocin vs Oxytocin (nma)	0.68 (0.56, 0.84)
(pairwise)	0.67 (0.54, 0.83)
Carbetocin vs Oxytocin (nma)	0.75 (0.50, 1.13)
(pairwise)	0.83 (0.54, 1.27)
Ergometrine plus Oxytocin vs Oxytocin (nma)	0.69 (0.54, 0.89)
(pairwise)	0.70 (0.52, 0.93)
Ergometrine vs Ergometrine plus Oxytocin (nma)	1.80 (1.16, 2.80)
(pairwise)	na
Misoprostol vs Ergometrine plus Oxytocin (nma)	1.67 (1.28, 2.17)
(pairwise)	2.28 (1.52, 3.41)
Misoprostol plus Oxytocin vs Ergometrine plus Oxytocin (nma)	0.99 (0.72, 1.35)
(pairwise)	1.42 (0.80, 2.49)
Carbetocin vs Ergometrine plus Oxytocin (nma)	1.08 (0.68, 1.72)
(pairwise)	0.55 (0.18, 1.68)
Ergometrine vs Carbetocin (nma)	1.65 (0.96, 2.86)
(pairwise)	na
Misoprostol vs Carbetocin (nma)	1.53 (1.00, 2.33)
(pairwise)	na
Misoprostol plus Oxytocin vs Carbetocin (nma)	0.91 (0.57, 1.43)
(pairwise)	na
Ergometrine vs Misoprostol plus Oxytocin (nma)	1.81 (1.19, 2.76)
(pairwise)	na
Misoprostol vs Misoprostol plus Oxytocin (nma)	1.68 (1.33, 2.12)
(pairwise)	1.87 (1.15, 3.01)
Ergometrine vs Misoprostol (nma)	1.08 (0.74, 1.56)
(pairwise)	1.15 (0.71, 1.85)

1
Relative Risk (RR)

Figure 75. Cumulative rankograms comparing each of the uterotonic drugs for prevention of PPH $\geq$ 500 mL restricted to studies with an objective method of measuring blood loss.
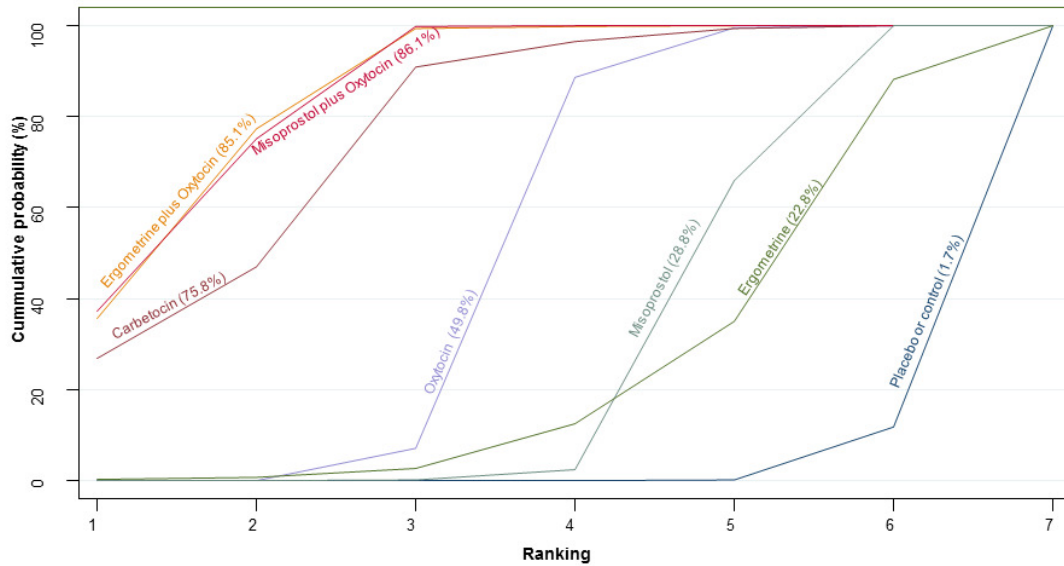
PPH $\geq$ 1000 mL

The network diagram for PPH $\geq$ 1000 mL for studies that used an objective method of measuring blood loss is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 49 trials suggested that all agents except carbetocin and ergometrine are effective for preventing PPH $\geq$ 1000 mL when compared with placebo or no treatment. Carbetocin demonstrated a similar trend towards reduction of this outcome (Appendix 3). Ergometrine plus oxytocin was found to be more effective when compared with the standard agent oxytocin. Ergometrine plus oxytocin was also found to be more effective than misoprostol and ergometrine when used alone. There was no evidence of global inconsistency in this analysis (P = 0.606). Appendix 3 shows the cumulative probabilities for each agent being at each possible rank for PPH $\geq$ 1000 mL for the studies that used an objective method of measuring blood loss. The highest ranked agent was ergometrine plus oxytocin. The ranking for carbetocin, oxytocin and misoprostol plus oxytocin was very close without a clear hierarchy.

Large studies only (> 400 participants)

PPH $\geq$ 500 mL

The network diagram for PPH $\geq$ 500 mL restricted to large trials with more than 400 participants is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 46 trials suggested that all agents except ergometrine are effective for preventing PPH $\geq$ 500 mL when compared with placebo or no treatment (Figure 76). Ergometrine plus oxytocin and misoprostol plus oxytocin were found to be more effective when compared with the standard agent oxytocin with carbetocin not being included in this analysis as there were no large studies comparing carbetocin to any of the other agents (Figure 76). Ergometrine plus oxytocin and misoprostol plus oxytocin were also found to be more effective than misoprostol and ergometrine when used alone. There was evidence of global inconsistency in this analysis (P = 0.011). However, we note that the CIs for both the network and direct evidence were overlapping across all comparisons suggesting locally-consistent results except for ergometrine versus placebo or no treatment based on a single study. Figure 77 shows the cumulative probabilities for each agent being at each possible rank for PPH $\geq$ 500 mL for large trials. The highest ranked agents were ergometrine plus oxytocin and misoprostol plus oxytocin. Oxytocin was ranked third and its probability in being ranked in the top two agents was close to 0%. Carbetocin could not be ranked as there were no studies found comparing it with any other agents in the network.

Figure 76.   Forest plot with relative risk ratios and 95% CIs from network meta-analysis and pairwise analyses for prevention of PPH $\geq$ 500 mL restricted to large studies (> 400 participants).
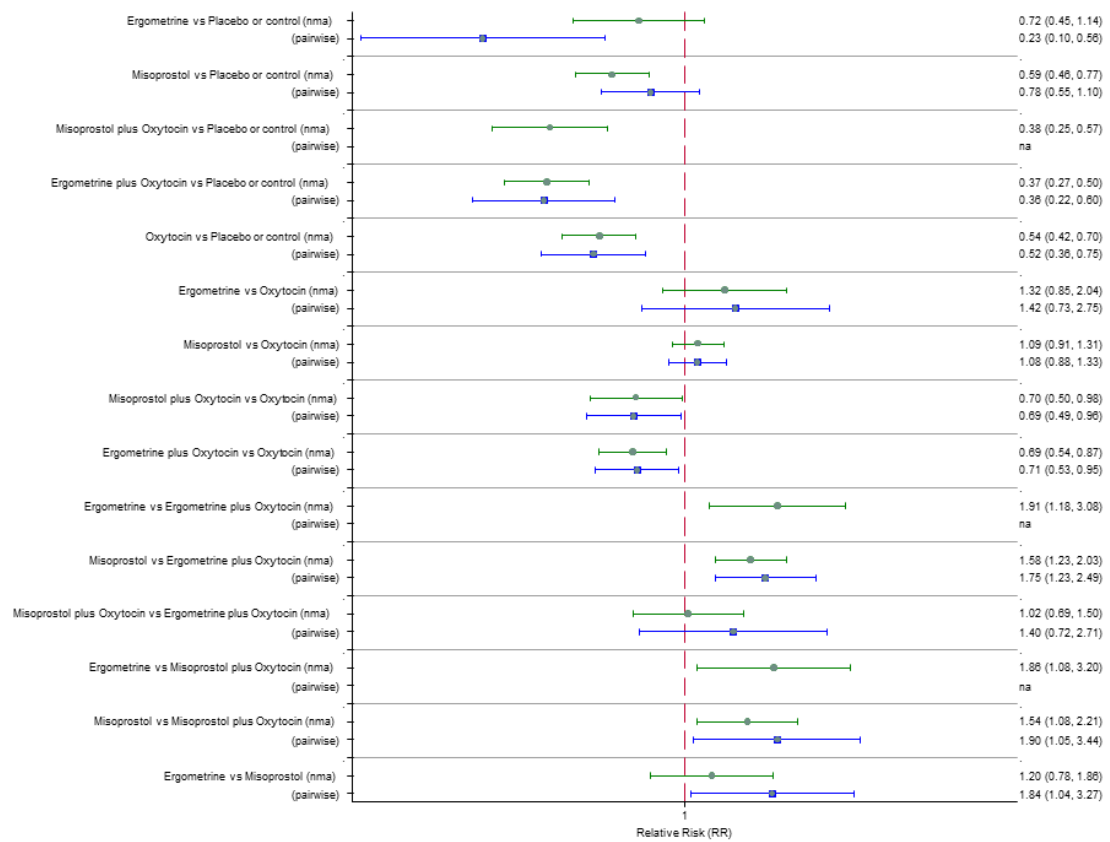
Figure 77. Cumulative rankograms comparing each of the uterotonic drugs for prevention of PPH ≥ 500 mL restricted to large studies (> 400 participants).
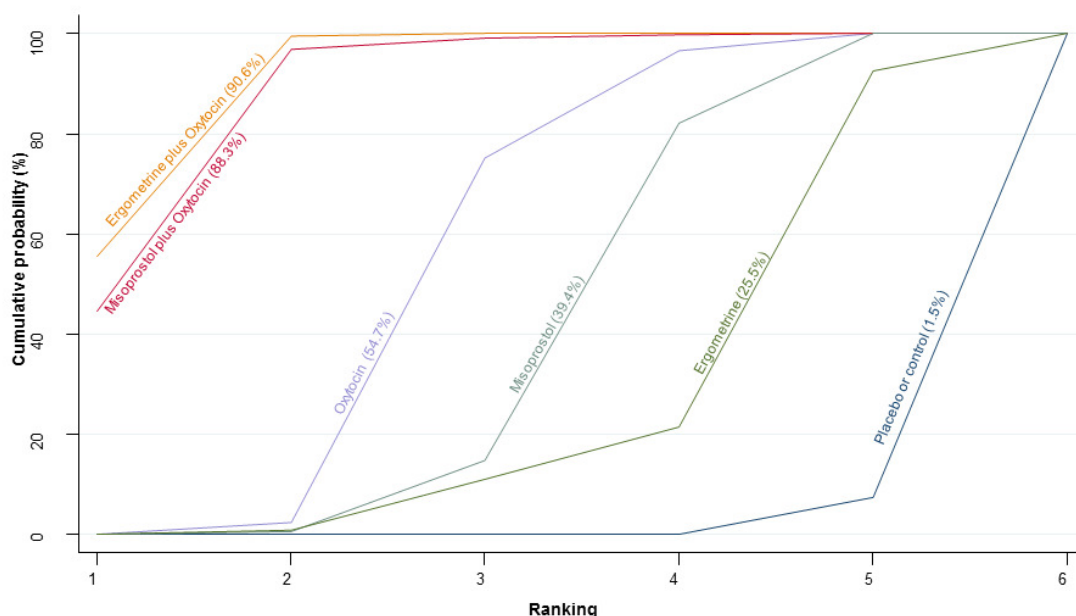
PPH ≥ 1000 mL

The network diagram for PPH ≥ 1000 mL restricted to large trials with more than 400 participants is presented in Appendix 2. Pooled effect estimates from the network meta-analysis of 46 trials suggested that all agents except ergometrine are effective for preventing PPH ≥ 500 mL when compared with placebo or no treatment (Appendix 3). Ergometrine plus oxytocin was found to be more effective when compared with the standard agent oxytocin with carbetocin not being included in this analysis as there were no large studies comparing carbetocin to any of the other agents (Appendix 3). Ergometrine plus oxytocin and oxytocin alone were also found to be more effective than misoprostol when used alone. There was no evidence of global inconsistency in this analysis (P = 0.122). Appendix 3 shows the cumulative probabilities for each agent being at each possible rank for PPH ≥ 1000 mL for the large trials. The highest ranked agents were ergometrine plus oxytocin and misoprostol plus oxytocin. Oxytocin was ranked third and its probability in being ranked in the top two agents was close to 10%. Carbetocin could not be ranked as there were no studies found comparing it with any other agents in the network.

Further sensitivity analyses

Further sensitivity analyses for the primary outcomes were performed by removing trials published earlier than 1990 (three trials), a cluster trial (one trial), removing trials with high level of missing data (10 trials) and removing trials where participants were also randomised to co-agents such as uterine massage and/or early controlled cord traction (three trials). Sensitivity analyses were also performed according to the choice of relative effect measure (RR versus OR) and the statistical model (fixed-effect versus random-effects model). We found that the overall ranking did not vary and the confidence intervals of the relative effects did not substantially change. Of note is that the global inconsistency was substantially reduced when the trials randomising to co-interventions were removed (P = 0.218).

DISCUSSION

Summary of main results

This network meta-analysis found that an ergometrine plus oxytocin combination, carbetocin, and a misoprostol plus oxytocin combination were more effective uterotonic drugs for preventing postpartum haemorrhage (PPH) ≥ 500 mL than the standard drug recommendation of oxytocin. An ergometrine plus oxytocin combination was also more effective in preventing PPH ≥ 1000 mL while a trend was noted for carbetocin and a misoprostol plus oxytocin combination. However, there was a higher risk of significant side-effects with the two combination regimens. Carbetocin

had a favourable side-effect profile similar to oxytocin. However, carbetocin trials were small and at high risk of bias, and when we restricted the analysis including only trials at low risk of bias, carbetocin lost its top ranking, although there was significant uncertainty around the effect estimates.

Overall completeness and applicability of evidence

This network meta-analysis provides the relative effectiveness of all drugs used for the prevention of PPH in a coherent and methodologically robust way across important clinical outcomes by combining both direct and indirect evidence, thus increasing the statistical power and confidence in the results. We found that most of the included trials reported our primary outcomes and most of the secondary outcomes. This increased the power across most of our analyses and contributed to the consistency in the ranking across all blood loss outcomes. We were thorough in our evaluation of the important potential treatment effect modifiers (mode of birth, prior risk of PPH, healthcare setting, dose, route and regimen of the drugs). We did not encounter important differences in the distribution of the effect modifiers between the different comparisons. In addition, the ranking of the drugs in each of the subgroups was comparable with the overall ranking. The results of the network meta-analyses were mostly consistent and where there was significant inconsistency this was likely due to unstable estimates from single studies. Through our sensitivity analyses we were able to identify that research underpinning the carbetocin effectiveness is based on small studies at high risk of bias.

Many trials excluded women with significant comorbidities and at very high risk for PPH. Women recruited to the included studies were predominantly delivered at more than 37 weeks of gestation. Most of the trials were carried out in hospital settings and with women having a vaginal birth. For women having a vaginal birth, uterotonic drug administration used to be a component of the active management of the third stage of labour, alongside controlled cord traction and early cord clamping. The most up-to-date guidelines from the WHO (WHO 2012), place emphasis on the administration of a uterotonic drug as the main agent within this package for prevention of PPH. These guidelines state that early cord clamping is generally not advised, whilst controlled cord traction is optional where skilled birth attendants are present (WHO 2012). Rankings of the available agents were similar in subgroups including only trials of women having a vaginal birth or undergoing a caesarean section, but there were no trials that used ergometrine plus oxytocin or ergometrine alone for prevention of PPH at caesarean section births. For women undergoing caesarean deliveries, the risk of PPH ≥500 mL was reduced from 75% with oxytocin down to almost 50% with more effective agents. Evidently, uterine tone plays a major role in PPH at caesarean section, with a relative reduction of PPH ≥500 mL similar to the one of women undergoing vaginal births when more effective agents are

used. The ranking is relevant to women at either high or low risk for PPH in hospital settings. There were not enough trials to be able to recommend a ranking in community settings, even though a similar ranking in terms of effectiveness can be expected.

The dosages, regimens and routes of drug administration for the most effective drugs varied. Carbetocin in most of the studies was administered as a single intravenous bolus of 100 mcg (15 studies) or intramuscularly (seven studies). The combination of ergometrine plus oxytocin was usually administered intramuscularly combining 500 mcg of ergometrine plus 5 IU (international units) of oxytocin (21 studies). Misoprostol plus oxytocin combinations varied greatly, with some studies administering an intravenous infusion of 20 IU of oxytocin and 400 mcg of misoprostol sublingually (three studies), or 200 mcg of misoprostol sublingually (two studies), others administering an intravenous bolus of oxytocin of 10 IU plus 400 mcg misoprostol sublingually (two studies) while others administered an intravenous infusion of 10 IU of oxytocin and 400 mcg of misoprostol rectally (two studies). There were another 12 ways of administering the oxytocin plus misoprostol combination described and each was employed in only one included study (see Characteristics of included studies).

Quality of the evidence

The majority of included trials were at uncertain risk of bias, with more than half of the quality domains not reported. We did not downgrade the estimates from the network meta-analysis involving combinations of either ergometrine or misoprostol plus oxytocin due to risk of bias (See Summary of findings for the main comparison). However, we regarded risk of bias from studies contributing to carbetocin comparisons to warrant downgrading for PPH ≥ 500 mL and PPH ≥ 1000 mL. We considered serious imprecision to warrant downgrading the quality of evidence for PPH ≥ 500 mL for carbetocin and for PPH ≥1000 mL for the combination of misoprostol plus oxytocin, and for carbetocin. We also downgraded the quality of the evidence for PPH ≥ 500 mL for ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin because of inconsistency in the comparisons with oxytocin.

Potential biases in the review process

The earliest included trial was conducted in 1976 (Moodie 1976), and in the decades since then, the clinical care and the clinical response to PPH may have improved. These temporal changes could have contributed to heterogeneity and increased the uncertainty of findings. However, we carried out a sensitivity analysis by removing trials published before 1990 and this did not vary the ranking of the drugs. As objective methods of measuring blood loss became increasingly available this could perhaps have also led to apparent changes in reported blood loss. The trials included

in the review recruited women with varied clinical characteristics, and it is important to consider this when interpreting results. The inclusion criteria were not always reported in detail and, when they were, these varied across trials. Further heterogeneity may also be present in the overall analysis related to the dose, route or regimen of the drugs. Even though we did not observe subgroup effects when we examined the dose of misoprostol or regimen of oxytocin administration, we were not able to perform subgroup analyses for every single increment in dosage or route of drug administration. Lastly, not all trials reported data on side-effects hence these analyses were often underpowered.

Agreements and disagreements with other studies or reviews

Our results agree with existing Cochrane reviews (Begley 2015; Liabsuetrakul 2007; McDonald 2004; Su 2012; Tuncalp 2012; Westhoff 2013) that focus on the comparison of a uterotonic drug versus another (direct comparisons). However, this network meta-analysis has several more studies than included in the previous reviews because of its nature of comparing all available uterotonic drugs in one single analysis and because it is the most up-to-date including recently published trials. Hence, some estimates differ slightly, as expected.

AUTHORS' CONCLUSIONS

Implications for practice

The current WHO recommendation for preventing PPH is 10 IU of intramuscular or intravenous oxytocin (WHO 2012). Oxytocin should be kept refrigerated (2 °C to 8 °C) or stored at room temperature (25 °C or lower). Several studies have demonstrated that oxytocin loses potency if stored at room temperature for too long or at higher temperatures, making its use difficult in low-resource countries (Hogerzeil 1993; WHO 1993). Since we have shown that oxytocin is ranked fourth in effectiveness, and and ergometrine plus oxytocin combination, carbetocin, and misoprostol plus oxytocin combination are more effective, our results could have important implications for clinical practice. Ergometrine plus oxytocin combination is the only agent that significantly reduces PPH ≥ 500 mL and PPH ≥ 1000 mL compared with oxytocin on both network and pairwise estimates. Misoprostol plus oxytocin combination evidence is less consistent and this may be related to the different routes and doses of misoprostol used in the studies. Carbetocin is more effective compared with oxytocin with a similar side-effect profile to oxytocin. However, when we restricted our analysis to trials with low risk of bias, the ranking of carbetocin changed and it did not appear to be more effective than oxytocin.

The manufacturer of carbetocin (Ferring Pharmaceuticals) has recently developed a room temperature stable (RTS) formulation, which makes it an attractive option for countries where maintaining the cold chain is problematic. Therefore, we conclude that there is an urgent need for a high-quality large trial comparing the current standard of oxytocin with carbetocin, and especially RTS carbetocin, to confirm or reject the findings of small and at high risk of bias trials that have involved carbetocin to date.

Implications for research

There are two key studies that will inform a future update of this review. The first one is a WHO-led multi-centre phase III clinical study comparing the effectiveness of RTS carbetocin versus oxytocin (administered intramuscularly) for the prevention of PPH among women having a vaginal birth (Widmer 2016). This trial is led by several of the study authors (MW, MG, JH and AC) and includes approximately 30,000 women from 10 countries: Argentina, Egypt, India, Kenya, Nigeria, Singapore, South Africa, Thailand, Uganda, and the UK. Results are expected before the end of 2018. If the results of the study support carbetocin, the aim is to provide access to RTS carbetocin to public sector providers in low-income countries with a high burden of maternal mortality, at an affordable and sustainable price comparable to oxytocin. Another trial based in the UK is recruiting more than 6000 women to a three-arm trial comparing carbetocin, oxytocin and ergometrine plus oxytocin combination (Draycott 2014). This trial is also expected to report in 2018. These trials will provide the high-quality evidence needed to update our network meta-analysis.

Consultation with our consumer group has demonstrated a need for more research into PPH outcomes identified as priorities for women and their families, such as women's views regarding the drugs used, clinical signs of excessive blood loss, neonatal unit admissions and breastfeeding at discharge. Trials to date have rarely investigated these outcomes. Consumers also considered the side-effects of uterotonic drugs to be important and these were often not reported. The Postpartum Haemorrhage Core Outcome Sets Project (http://www.comet-initiative.org/studies/details/706) will elucidate outcomes to prioritise in trial reporting and will inform futures updates of this review. We would urge all trialists to consider reporting these outcomes for each drug in all future randomised trials. Lastly, future evidence synthesis research could compare the effects of different dosages and routes of administration for the most effective drugs.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Abdel-Aleem 2010

Methods	3-arm controlled randomised trial.
Participants	Between September 2006 and February 2009, 1964 parturients were randomised in a hospital setting in Egypt and South Africa. The population comprised women of unspecified parity, either singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients with medical complications such as hypertension and diabetes, previous caesarean section, or an abdominal wall that was not thin enough to allow easy palpation of the uterus after delivery
Interventions	10 IU of oxytocin administered intramuscularly (n = 1302) versus placebo or control (n = 662)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, additional uterotonics, transfusion, manual removal of placenta. death
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were allocated to 1 of 3 groups by selecting the next number in a computer-generated random number sequence
Allocation concealment (selection bias)	Low risk	The allocated group was noted inside opaque sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and caregivers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Low risk	In Assiut, investigators evaluated blood loss by collection with a calibrated plastic drape placed under the mother within 30 minutes of delivery. At the East London Hospital Complex, investigators evaluated blood loss by collection with a low profile plastic "fracture" bedpan placed under the

		mother
Incomplete outcome data (attrition bias) All outcomes	Low risk	Investigators were unable to collect outcome data from 14 randomised study participants
Selective reporting (reporting bias)	Unclear risk	The study protocol was registered retrospectively (ACTRN: 12609000372280)
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by funding from the institution of the authors, or conducted without external funding

Acharya 2001

Methods	2-arm active-controlled randomised trial.
Participants	Between dates unspecified, 60 parturients were randomised in a hospital setting in the UK. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at high risk for PPH, who delivered by elective caesarean section. Exclusion criteria were not specified
Interventions	10 IU of oxytocin administered by an intravenous bolus (n = 30) versus 400 mcg of misoprostol administered orally (n = 30)
Outcomes	The study recorded the following outcomes: PPH at 1000, additional uterotonics, transfusion, blood loss (mL), change in Hb level, vomiting, shivering
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Low risk	Randomisation was performed using sealed opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and caregivers) was not reported

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	High risk	Investigators evaluated intra-operative blood loss by the estimation of attending physicians, and by measurement of preoperative and postoperative Hb concentration and haematocrit
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Adanikin 2012

Methods	2-arm active-controlled double-dummy randomised trial.
Participants	Between 1st July 2010 and 31st March 2011, 218 parturients were randomised in a hospital setting in Nigeria. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at high risk for PPH, who delivered by elective caesarean section. Exclusion criteria comprised parturients with altered serum electrolytes, peritonitis, sepsis, previous bowel surgery, thyroid disease, inflammatory bowel disease, or chronic constipation
Interventions	25 IU of oxytocin administered by an intravenous bolus plus infusion (n = 109) versus 600 mcg plus 5 IU of misoprostol plus oxytocin administered rectally plus by an intravenous bolus (n = 109)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, blood loss (mL) , nausea, vomiting, fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	The treatment allocation sequence was developed by 1 researcher (O.O.) using a computer-generated table of random numbers with varied permutated blocks
Allocation concealment (selection bias)	Low risk	Investigators used sealed opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The same researcher administered the drugs intra-operation and set up the infusions in the operating room; he was the only person who was not blind to the drug allocation and he did not take any further part in the active running of the study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Unclear risk	Methods of evaluating blood loss were not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Afolabi 2010

Methods	2-arm active-controlled randomised trial.
Participants	Between dates unspecified, 200 parturients were randomised in a hospital setting in Nigeria. The population comprised women of parity 4 or less, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing induction of labour or caesarean section, or those with haematocrit of less than 30%, pre-eclampsia/eclampsia, grand multiparity (5 or more), multiple pregnancy, coagulopathy, or medical disorders
Interventions	10 IU of oxytocin administered intramuscularly (n = 100) versus 400 mcg of misoprostol administered orally (n = 100)

Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, additional uterotonics, transfusion, manual removal of placenta, death, blood loss (mL), change in Hb, third-stage duration (min), nausea, vomiting, fever, shivering
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised into 2 groups, A and B, by blocked (restrictive) double-blind randomisation using random table generated numbers
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and caregivers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss at delivery by collection with a large kidney dish, for measurement in a graduated measuring jar
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Ahmed 2014

Methods	2-arm active-controlled randomised trial.
Participants	Between dates unspecified, 80 parturients were randomised in a hospital setting in Egypt. The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by either elective or emergency caesarean. Exclusion criteria comprised parturients with risk factors for excessive blood loss e.g. those with placenta praevia or placental abruption
Interventions	100 mcg of carbetocin administered by an intravenous bolus (n = 40) versus 10 IU of oxytocin administered by an intravenous bolus (n = 40)
Outcomes	The study recorded the following outcomes: blood loss (mL).
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study was "single-blind" but the identity of those blinded and the method of blinding were not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Unclear risk	Methods of evaluating blood loss were not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised

Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Al-Sawaf 2013

Methods	3-arm controlled randomised trial.
Participants	Between October 2009 and February 2011, 120 parturients were randomised in a hospital setting in Egypt. The population comprised women of parity 4 or less, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing induction of labour or instrumental delivery, or those with previous caesarean section, extensive perineal, vaginal or cervical lacerations, bleeding disorders, Hb less than 100 g/L, uterine malformations, grand multiparity, multiple pregnancy, polyhydramnios, intrauterine fetal death, medical problems such as pre-eclampsia, diabetes, cardiopulmonary problems, bowel disease, or allergy to prostaglandins
Interventions	Placebo or control (n = 40) versus 200 mcg of misoprostol administered sublingually (n = 40) versus 5 IU of oxytocin administered intramuscularly (n = 40)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, blood loss (mL), change in Hb level
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Investigators used closed envelopes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding (of study participants and caregivers) was not reported
Objective assessment of blood loss	Low risk	Assessor blinding was not reported.

Incomplete outcome data (attrition bias) All outcomes	High risk	Investigators evaluated blood loss by collection with sterile packs weighed beforehand and afterwards
Selective reporting (reporting bias)	Unclear risk	"Following randomisation, 16 study participants were excluded from our analysis. Of these, 14 patients received intrapartum oxytocin, 1 patient experienced extensive vaginal laceration and another experienced a cervical laceration."
Intention to treat analysis	High risk	The protocol of the study was unavailable for verification.
Funding source	Unclear risk	Those who withdrew from the study after randomisation were not included in the analysis

Amant 1999

Methods	2-arm active-controlled double-dummy randomised trial.
Participants	Between 1st December 1997 and 20th April 1998, 213 parturients were randomised in a hospital setting in Belgium. The population comprised women of unspecified parity, either singleton or multiple pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing caesarean section, or those with hypertensive disorders, gestational age less than 32 weeks, intrauterine fetal death, uterine malformations, inflammatory bowel disease, obliterative vascular or coronary disease, sepsis, allergy to prostaglandins or alkaloids
Interventions	600 mcg of misoprostol administered orally (n = 105) versus 200 mcg of ergometrine administered by an intravenous bolus (n = 108)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonic, transfusion, manual removal of placenta, nausea, vomiting, headache, fever, shivering
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment was allocated by a computer-generated list and randomisation in blocks
Allocation concealment (selection bias)	Low risk	The study box contained either 2 capsules of misoprostol and an ampoule containing placebo, or 2 capsules with placebo and an

Amant 1999 *(Continued)*

		ampoule containing methylergometrine. The study boxes and capsules were indistinguishable in the 2 groups
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study participants and caregivers were blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Unclear risk	Methods of evaluating blood loss were not reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	"213 women were enrolled in the study, but the data for 13 were excluded because a caesarean section was performed after randomisation (n = 3), or because no predelivery (n = 3) or postpartum (n = 7, short hospital stay) blood sample was taken."
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	High risk	Those who withdrew from the study after randomisation were not included in the analysis
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Amin 2014

Methods	2-arm active-controlled randomised trial.
Participants	Between May 2011 and May 2012, 200 parturients were randomised in a hospital setting in Pakistan. The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing caesarean section, or those with traumatic PPH, bleeding disorders, prolonged labour, placenta praevia, placental abruption, multiple pregnancy, BMI more than 30, or previous PPH
Interventions	5 IU of oxytocin administered by an intravenous bolus (n = 100) versus 800 mcg of misoprostol administered rectally (n = 100)
Outcomes	The study recorded the following outcomes: PPH at 500, morbidity, manual removal of placenta, death, blood loss (mL), third-stage duration (min), vomiting, fever, shivering

Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and care-givers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by collection with special drapes placed under the mother until 1-hour postpartum, and weighed beforehand and afterwards. Blood was also collected in graduated plastic bags
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Askar 2011

Methods	2-arm active-controlled double-blinded randomised trial.
Participants	Between May 2009 and December 2009, 240 parturients were randomised in a hospital setting in Kuwait. The population comprised women of parity 5 or less, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients less than 18 years old and those with known or suspected co-agulopathy, grand multiparity (5 or more), uterine fibroids, polyhydramnios, multiple pregnancy, fetal macrosomia, severe anaemia, cervical tears or who required prophylactic oxytocin infusion. The presence of contraindications for the use of either Syntometrine or carbetocin that include pre-existing hypertension, pre-eclampsia, asthma, cardiac, renal or liver diseases, epilepsy, or history of hypersensitivity to Syntometrine or carbetocin
Interventions	100 mcg of carbetocin administered intramuscularly (n = 120) versus 5 IU and 500 mcg of ergometrine plus oxytocin administered intramuscularly (n = 120)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, manual removal of placenta, blood loss (mL), change in Hb level, nausea, vomiting, hypertension, headache, abdominal pain
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment was allocated by a computer-generated code prepared before the recruitment
Allocation concealment (selection bias)	Low risk	Investigators used sealed, consecutively-numbered, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study participants and caregivers were blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by collection with a new plastic sheet placed under the mother following delivery of the placenta, and weighed (together with any gauzes, tampons and pads applied during the delivery) beforehand and 2 hours afterwards. A digital scale was used for weight measurement

Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Attilakos 2010

Methods	2-arm active-controlled double-blinded randomised trial.
Participants	Between November 2006 and July 2007, 377 parturients were randomised in a hospital setting in the UK. The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by either elective or emergency caesarean. Exclusion criteria comprised parturients undergoing caesarean section with general anaesthesia, gestational age less than 37 weeks performed for fetal or maternal distress where, due to time constraints, it was not possible to recruit or randomise, or those with multiple pregnancy, placenta praevia or placental abruption
Interventions	100 mcg of carbetocin administered by an intravenous bolus (n = 188) versus 5 IU of oxytocin administered by an intravenous bolus (n = 189)
Outcomes	The study recorded the following outcomes: PPH at 1000, morbidity,. additional uterotonics, transfusion, death, blood loss (mL), change in Hb level, nausea, vomiting, headache, tachycardia, hypotension, shivering, abdominal pain
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation sequence (1:1 ratio-blocks of 10, no stratification) was generated by computer
Allocation concealment (selection bias)	Low risk	The preparation of the ampoules was undertaken by DHP Ltd. (Powys, UK) which provided sequentially numbered and labelled boxes each containing a 1 mL am-

		poule of the study drug. All boxes and ampoules were identically labelled, with the study number being the only differentiating feature between different drug packs. The random allocation sequence was not known to the investigators until the study had finished and the analysis was started
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study participants and caregivers were blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	High risk	Blood loss was estimated by the attending surgeon "in the usual way (visual estimation, number of used swabs and amount of aspirated blood)."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Low risk	The study report matches the study protocol that was registered prospectively (EudraCT 2005-002812-94)
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	Ferring Pharmaceuticals funded the cost of preparation of blinded medication ampoules. No other external funding was required for the study

Atukunda 2014

Methods	2-arm active-controlled double-dummy randomised trial.
Participants	Between 23rd September 2012 and 9th September 2013, 1140 parturients were randomised in a hospital setting in Uganda. The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing induction or augmentation of labour or elective caesarean section, or those with intrauterine fetal death, heart disease, severe malaria or acute bacterial infection, multiple pregnancy, antepartum haemorrhage, altered cognitive status or reported hypersensitivity to prostaglandins

Interventions	10 IU of oxytocin administered intramuscularly (n = 570) versus 600 mcg of misoprostol administered sublingually (n = 570)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, additional uterotonics, transfusion, manual removal of placenta, death, blood loss (mL) , change in Hb level.. third-stage duration (min), nausea, vomiting, headache, fever, shivering, abdominal pain
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A study biostatistician generated a randomisation list with a block size of 10
Allocation concealment (selection bias)	Low risk	The study clinical pharmacist prepared the study drugs and placebos. The midwife research assistants received opaque envelopes with affixed study codes, containing both an injection (1 mL of oxytocin 10 IU or its placebo) and 3 pills (misoprostol 600 mg or its placebo)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"To achieve blinding of the participants and assessors, both inactive agents were manufactured and packaged to resemble actual study medicines in terms of shape, size, and colour."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by collection with a clean plastic sheet placed under the mother during and after the third stage of labour. The sheet was specifically designed and piloted for the purpose. Blood was then drained into a calibrated container to improve accuracy in blood loss measurement. Furthermore, "mothers were given pre-weighed standard sanitary pads to place in the perineum at all times. These pads were changed and weighed hourly for the

		first 6 hours, and then every 6 hours until 24 hours postpartum. Blood loss was estimated as 1 mL per g of weight of the pad after subtracting the dry pad weight." Investigators added the estimated blood loss in pads, to the volume of blood already collected with the plastic sheet. To improve consistency in the estimation of blood loss, standardised electronic scales were used to weigh soiled sanitary pads
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Low risk	The study report matches the study protocol that was registered (ClinicalTrials.gov NCT01866241)
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by scholarship funding from the Father Bash Foundation (public funding)

Badejoko 2012

Methods	2-arm active-controlled double-dummy randomised trial.
Participants	Between 1st April 2009 and 31st December 2009, 264 parturients were randomised in a hospital setting in Nigeria. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at high risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients in the second or third stage of labour, or those with cervical lacerations or coagulopathy
Interventions	30 IU of oxytocin administered by an intravenous bolus plus infusion (n = 132) versus 20 IU plus 600 mcg of misoprostol plus oxytocin administered rectally plus by an intravenous infusion (n = 132)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, additional uterotonics, transfusion, death, blood loss (mL), vomiting, fever, shivering
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation code produced by an independent statistician using a computer-generated random number sequence
Allocation concealment (selection bias)	Low risk	Investigators used sequentially numbered sealed packets made of identical opaque brown-paper envelopes prepared by the hospital pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study participants and caregivers were blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by collection with a BRASS-V calibrated drape "which is a sterile intrapartum blood collection mat with a calibrated receptacle" placed under the mother after the delivery of the baby and immediate clamping of the umbilical cord. The drape included ribbons tied around the abdomen of the mother to optimise blood collection
Incomplete outcome data (attrition bias) All outcomes	Low risk	"6 women from the misoprostol group and 3 from the oxytocin group were excluded from statistical analysis. 5 of these women in the misoprostol group and all 3 in the oxytocin group were excluded because of the occurrence of cervical lacerations in them. The sixth woman excluded in the misoprostol group had developed features of disseminated intravascular coagulopathy (DIC). Analysis was thus based on 255 parturients (126 in the misoprostol group and 129 in the oxytocin group)."
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	High risk	Those who withdrew from the study after randomisation were not included in the analysis

Badejoko 2012 (*Continued*)

Funding source	Low risk	The study was conducted without external funding.

Balki 2008

Methods	2-arm active-controlled double-blinded randomised trial.
Participants	Between 12th June 2005 and 18th December 2006, 48 parturients were randomised in a hospital setting in Canada. The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by emergency caesarean section. Exclusion criteria comprised parturients requiring general anaesthesia, or those with cardiac disease, hypertension or any condition predisposing to uterine atony and PPH, such as placenta praevia, multiple pregnancy, pre-eclampsia, macrosomia, polyhydramnios, uterine fibroids, bleeding disorders, chorioamnionitis, previous uterine atony, previous PPH or allergy/hypersensitivity to oxytocin or ergot derivatives
Interventions	250 mcg plus 20 IU of ergometrine plus oxytocin administered by an intravenous bolus (n = 24) versus 20 IU of oxytocin administered by an intravenous bolus plus infusion (n = 24)
Outcomes	The study recorded the following outcomes: additional uterotonics, transfusion, blood loss (mL), nausea, vomiting, hypertension, tachycardia. hypotension
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using a computer-generated list of numbers
Allocation concealment (selection bias)	Low risk	Investigators used consecutively-numbered opaque sealed packets or envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study participants and caregivers were blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss by measurement of haematocrit preoperatively and 48 hours postoperatively

Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by funding from the institution of the authors

Bamigboye 1998a

Methods	2-arm placebo-controlled randomised trial.
Participants	Between dates unspecified, 550 parturients were randomised in a hospital setting in South Africa. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria were not specified
Interventions	400 mcg of misoprostol administered rectally (n = 275) versus placebo or control (n = 275)
Outcomes	The study recorded the following outcomes: PPH at 1000, additional uterotonics, manual removal of placenta, third-stage duration (min), vomiting, shivering, abdominal pain
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using a computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Allocation concealment was by means of sealed, opaque containers containing 400 mg misoprostol or placebo tablets
Blinding of participants and personnel (performance bias) All outcomes	High risk	"The placebo tablets were similar in size and colour but were not identical in shape to the misoprostol tablets. Blinding of the midwife administering the tablets was

Bamigboye 1998a *(Continued)*

		therefore not possible."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by collection with an absorbent plastic-backed linen saver and a low-profile plastic "fracture" bedpan placed under the mother. Blood collection in the plastic bedpan continued until 1 hour after delivery of the baby. At 1 hour after delivery, all the blood on the linen saver was scooped into the bedpan with the blood already collected there, and "the total blood was carefully measured." All the used linen savers and vaginal pads were weighed, and the known dry weights of these materials were subtracted from the measured total weight
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Records of 4 of the 550 allocations (all from the placebo group) could not be traced."
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Bamigboye 1998b

Methods	2-arm active-controlled randomised trial.
Participants	Between dates unspecified, 491 parturients were randomised in a hospital setting in South Africa. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria were not specified
Interventions	400 mcg of misoprostol administered rectally (n = 241) versus 500 mcg and 5 IU respectively of ergometrine plus oxytocin administered intramuscularly (n = 250)

Outcomes	The study recorded the following outcomes: PPH at 500, additional uterotonics, transfusion, manual removal of placenta, blood loss (mL), change in Hb level third-stage duration (min)
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using a computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Allocation concealment was by means of sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and caregivers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss by the estimation of attending physicians
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"About halfway through enrolment it was discovered that a small number of women had been excluded from the Syntometrine [ergometrine plus oxytocin] group because of hypertension detected after enrolment (thus contraindicating the use of Syntometrine [ergometrine plus oxytocin]. The Syntometrine envelopes had been reallocated to subsequent participants, and it was not possible to trace the women originally allocated."
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised

Bamigboye 1998b *(Continued)*

Funding source	Low risk	The study was supported by funding from the South African Medical Research Council (public funding)

Barton 1996

Methods	2-arm placebo-controlled randomised trial.
Participants	Between dates unspecified, 119 parturients were randomised in a hospital setting in the USA. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at high risk for PPH, who delivered by elective caesarean section. Exclusion criteria were not specified
Interventions	100 mcg of carbetocin administered by an intravenous bolus (n = 62) versus placebo or control (n = 57)
Outcomes	The study recorded the following outcome: additional uterotonics
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and caregivers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Unclear risk	Methods of evaluating blood loss were not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.

Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Baskett 2007

Methods	2-arm active-controlled double-dummy randomised trial.
Participants	Between October 2000 and February 2004, 622 parturients were randomised in a hospital setting in Canada. The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing caesarean section, or those with placenta praevia, placental abruption, coagulopathy or unstable asthma
Interventions	5 IU of oxytocin administered by an intravenous bolus (n = 311) versus 400 mcg of misoprostol administered orally (n = 311)
Outcomes	The study recorded the following outcomes: PPH at 1000, additional uterotonics, transfusion, manual removal of placenta, death, fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation cards were produced.
Allocation concealment (selection bias)	Low risk	Investigators used sealed, opaque, sequentially numbered envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The packages were prepared by the hospital pharmacy and their active drug unknown to the physicians and nurses."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.

Objective assessment of blood loss	High risk	Investigators evaluated blood loss by a combination of the visual estimation of attending physicians and measurement of blood volume in a kidney dish placed under the mother during the third stage of labour
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by funding from the Nova Scotia Health Research Foundation (public funding)

Begley 1990

Methods	2-arm controlled randomised trial.
Participants	Between 1st October 1987 and 31st October 1988, 1429 parturients were randomised in a hospital setting in Ireland. The population comprised women of parity 5 or less, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing caesarean section, vaginal breech or instrumental delivery, or those with hypertension, epidural anaesthesia, antepartum haemorrhage, placenta praevia, placental abruption, first stage of labour more than 15 hours, "quick" delivery or needing resuscitation
Interventions	500 mcg of ergometrine administered by an intravenous bolus (n = 705) versus placebo or control (n = 724)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, manual removal of placenta, blood loss (mL), change in Hb level. third-stage duration (min), nausea, vomiting, hypertension, headache, aAbdominal pain
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Random number tables were used. The first number was selected from the table and the numbers were then allocated in blocks of 100, following in sequence
Allocation concealment (selection bias)	Low risk	Investigators used numbered, sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study participants and caregivers were not blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessors were not blinded to treatment allocations.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss "as accurately as possible, with full realisation of the well-documented problems of clinical measuring and estimation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses but dropouts for change in Hb
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by public funding, or conducted without external funding

Bellad 2012

Methods	2-arm active-controlled double-dummy randomised trial.
Participants	Between dates unspecified, 652 parturients were randomised in a hospital setting in India. The population comprised women of unspecified parity, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing caesarean section or instrumental delivery, or those with medical disorders, in active labour with more than 4 cm dilatation or stillbirths
Interventions	400 mcg of misoprostol administered sublingually (n = 321) versus 10 IU of oxytocin administered intramuscularly (n = 331)

Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, additional uterotonics, transfusion, manual removal of placenta, death, blood loss (mL), third-stage duration (min), nausea, vomiting, fever, shivering, abdominal pain
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were assigned to treatment with a 1:1 ratio using computer-generated simple randomisation
Allocation concealment (selection bias)	Low risk	The study medications and placebos were packaged in appropriately coded envelopes by administrative staff from the department of clinical pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study participants and caregivers were blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by collection with a BRASS-V calibrated drape placed under the mother before delivery of the baby. "The calibrated blood collection receptacle was opened after delivery and drainage of amniotic fluid. The blood collected in the drape was transferred to a measuring jar with 10 mL calibrations for accuracy. Blood-soaked swabs were weighed in g, and the known dry weight of the swabs was subtracted; this volume was added to the measured blood volume from the drape (assuming an equivalence of 1 g and 1 mL)." Blood loss was measured at 1 and 2 hours after delivery of the baby
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants

Bellad 2012 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	The study protocol was registered retrospectively (ClinicalTrials.gov NCT01373359)
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by funding from Jawaharlal Nehru Medical College (the institution of the authors). Study medications were donated by Cipla (misoprostol) and AstraZeneca (oxytocin)

Benchimol 2001

Methods	3-arm controlled randomised trial.
Participants	Between November 1999 and June 2000, 602 parturients were randomised in a hospital setting in France. The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing caesarean section, or those with gestational age less than 32 weeks, previous PPH, intrauterine fetal death, previous uterine scar, multiple pregnancy or pre-eclampsia
Interventions	Placebo or control (n = 220) versus 2.5 IU of oxytocin (n = 196) administered intramuscularly versus 600 mcg of misoprostol administered orally (n = 186)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, blood loss (mL), change in Hb level, vomiting, fever, shivering
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Slips with the words "control," "Syntocinon," and "Cytotec" were placed into envelopes which were then drawn at random upon admission into the delivery room to determine to which group the woman would belong
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and caregivers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by weighing (methods of collecting blood were not reported)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Bhullar 2004

Methods	2-arm placebo-controlled randomised trial.
Participants	Between October 2000 and December 2002, 756 parturients were randomised in a hospital setting in the USA. The population comprised women of unspecified parity, either singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing caesarean section, or those with a bleeding disorder
Interventions	200 mcg plus 20 IU of misoprostol plus oxytocin administered sublingually plus by an intravenous infusion (n = 377) versus 20 IU of oxytocin administered by an intravenous infusion (n = 379)
Outcomes	The study recorded the following outcomes: PPH at 500, additional uterotonics, transfusion, manual removal of placenta, death, blood loss (mL), change in Hb level, third-stage duration (min), vomiting, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Agent vials were coded with a number, which had been assigned using a random number table
Allocation concealment (selection bias)	Low risk	Investigators used opaque vials containing either a 200 mcg misoprostol tablet or placebo
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"The placebo tablets were similar in size and colour, but not identical in shape to the misoprostol tablet."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"The placebo tablets were similar in size and colour, but not identical in shape to the misoprostol tablet."
Objective assessment of blood loss	High risk	Investigators evaluated blood loss by the estimation of attending physicians
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Borruto 2009

Methods	2-arm active-controlled randomised trial.
Participants	Between 1st September 2007 and 5th January 2008, 104 parturients were randomised in hospital settings in France and Italy. The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by either elective or emergency caesarean. Exclusion criteria comprised parturients with toxaemia, eclampsia or epilepsy
Interventions	100 mcg of carbetocin administered by an intravenous bolus (n = 52) versus 10 IU of oxytocin administered by an intravenous infusion (n = 52)

Outcomes	The study recorded the following outcomes: PPH at 500, additional uterotonics, blood loss (mL), vomiting, headache, hypotension, shivering, abdominal pain
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"The patients were divided in 2 groups with blinding to the study medication." Blinding of caregivers was unconfirmed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by "a sensitive colorimetric method."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	High risk	The authors "do not have a financial relationship with the organisation that sponsored the research." No other source(s) of funding for the study were reported

Boucher 1998

Methods	2-arm active-controlled double-dummy randomised trial.
Participants	Between dates unspecified, 60 parturients were randomised in a hospital setting in Canada. The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by elective caesarean section. Exclusion criteria comprised parturients with heart disease or cardiac arrhythmia, hypertension or liver/renal/ endocrine disease
Interventions	100 mcg of carbetocin administered by an intravenous bolus (n = 29) versus 32.5 IU of oxytocin administered by an intravenous bolus plus infusion (n = 28)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, death, blood loss (mL), nausea, vomiting, headache, fever, shivering, abdominal pain
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study participants and caregivers were blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by a sensitive colorimetric measurement of the Hb concentration of blood loss collected "by means of aspiration from the operative field [that] began immediately after administration of the study drug and ceased at the time of skin closure. All gauzes used during this timeframe were placed in 15% Lyse solution. All aspirated blood, gauzes, and the reference blood sample were sent to the laboratory for quantification of total blood volume. Blood on gauzes was extracted with Lyse solution, and Hb content was determined with a sensitive colorimetric

		method adapted to the Cobas FARA analyser. Haemoglobin concentration is proportional to the absorbance of a hydrogen peroxide-activated aminophenazone-phenol mixture measured at a wavelength of 500 nm. The inter-assay coefficient of variation averaged 3.3%, and the limit of detection of the assay was 14 mg/dL. The amount of blood collected in gauzes was calculated with the following formula: blood loss in dL = amount of Hb in surgical gauzes in mg /Hb concentration in mg/dL before caesarean section. Total blood loss was calculated by means of summing the volumes of blood aspirated and collected with gauzes."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"3 patients who received general instead of epidural anesthesia were excluded from the study and did not receive the study medication" but the study report did not specify whether these exclusions occurred before or after randomisation
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	High risk	Those who withdrew from the study after randomisation were not included in the analysis
Funding source	High risk	The study was supported by funding from Ferring Pharmaceuticals

Boucher 2004

Methods	2-arm active-controlled double-dummy randomised trial.
Participants	Between dates unspecified, 164 parturients were randomised in a hospital setting in Canada. The population comprised women of unspecified parity, either singleton or multiple pregnancy, at high risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients younger than 18 years old, or those without known PPH risk, known or suspected coagulopathy, heart disease or cardiac arrhythmia, chronic liver/ renal/endocrine disease or hypersensitivity to study drugs
Interventions	100 mcg of carbetocin administered intramuscularly (n = 84) versus 10 IU of oxytocin administered by an intravenous infusion (n = 80)

Outcomes	The study recorded the following outcomes: PPH at 500, additional uterotonics, blood loss (mL), change in Hb level, nausea, vomiting, headache, shivering, abdominal pain
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Investigators used computer-generated randomisation codes with a block size of 4
Allocation concealment (selection bias)	Unclear risk	Investigators used consecutively-numbered sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was "double-blind": "for each study subject, kits containing both the study medication and a placebo were prepared in the hospital pharmacy according to the randomisation schedule, to assure blinding of the clinical staff."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Unclear risk	Methods of evaluating blood loss were not reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	"4 women did not receive study medication and were therefore not included in the analysis (3 were excluded as a result of caesarean births). Had these 4 women completed the study and received the medication, 1 would have received carbetocin and 3 would have received oxytocin. This factor contributed to the lower reported number of women receiving oxytocin."
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	High risk	Those who withdrew from the study after randomisation were not included in the analysis

Boucher 2004 *(Continued)*

Funding source	High risk	The study was supported by funding from Ferring Pharmaceuticals

Bugalho 2001

Methods	2-arm active-controlled double-dummy randomised trial.
Participants	Between dates unspecified, 700 parturients were randomised in a hospital setting in Mozambique. The population comprised women of unspecified parity, either singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing induction or augmentation of labour
Interventions	400 mcg of misoprostol administered rectally (n = 350) versus 10 IU of oxytocin administered intramuscularly (n = 350)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, blood loss (mL), third-stage duration (min), vomiting, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Neither the investigators nor the nurses participating in the study had access to the codes until the completion of the study."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss with a metallic collector placed under the mother, from immediately after delivery of the baby until the mother was removed from the delivery room

Incomplete outcome data (attrition bias) All outcomes	Low risk	"A few subjects were excluded after randomisation for emergency caesarean section or incomplete data collection."
Selective reporting (reporting bias)	High risk	The protocol of the study was unavailable for verification, but not all of the outcomes projected by methodological descriptions were reported as results in the study report (cases of retained placenta were omitted)
Intention to treat analysis	High risk	Those who withdrew from the study after randomisation were not included in the analysis
Funding source	Low risk	This study was financed by the Maputo Central Hospital (the institution of the authors) and the Special Program on Research and Research Training in Human Reproduction of the WHO (public funding)

Butwick 2010

Methods	5-arm placebo-controlled randomised trial.
Participants	Between July 2008 and April 2009, 75 parturients were randomised in a hospital setting in the USA. The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by elective caesarean section. Exclusion criteria comprised parturients with active labour, ruptured membranes, drug allergy, multiple pregnancy, significant obstetric disease, risk factors for PPH (abnormal placentation, fibroids, previous PPH, previous classical uterine incision), coagulopathy or thrombocytopenia
Interventions	Placebo or control (n = 15) versus 5, 3, 1, or 0.5 IU of oxytocin administered by an intravenous bolus (n = 60)
Outcomes	The study recorded the following outcomes: additional uterotonics, transfusion, blood loss (mL), nausea, vomiting, tachycardia, hypotension
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using Microsoft Excel-generated random number

		allocations
Allocation concealment (selection bias)	Unclear risk	Investigators used opaque envelopes containing group assignments
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The obstetrician and anaesthetist involved in each case were blinded to the oxytocin dose assignments."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss "by estimating blood collected by suction and by calculating the weight of blood on surgical swabs."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"75 patients were enrolled, and 74 patients completed the study; 1 patient was excluded due to protocol violation (obstetrician request for supplemental oxytocin despite adequate uterine tone)."
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	High risk	Those who withdrew from the study after randomisation were not included in the analysis
Funding source	Low risk	The study was supported by funding from the Department of Anaesthesia of the Stanford University School of Medicine (the institution of the authors)

Caliskan 2002

Methods	4-arm active-controlled double-dummy randomised trial.
Participants	Between 1st January 2000 and 1st October 2000,1633 parturients were randomised in a hospital setting in Turkey. The population comprised women of unspecified parity, either singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing caesarean section, or those with gestational age less than 32 weeks or hypersensitivity to prostaglandins
Interventions	400 mcg plus 10 IU of misoprostol plus oxytocin administered rectally plus by an intravenous infusion (n = 407) versus 400 mcg of misoprostol administered rectally (n = 405) versus 10 IU of oxytocin administered by an intravenous infusion (n = 412) versus

	200 mcg plus 10 IU of ergometrine plus oxytocin administered intramuscularly plus by an intravenous infusion (n = 409)
Outcomes	The study recorded the following outcomes: PPH at 500. PPH at 1000, additional uterotonics, transfusion, change in Hb level, third-stage duration (min), vomiting, fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was based on a table of computer-generated blocks of random numbers
Allocation concealment (selection bias)	Low risk	Investigators used sealed consecutively-numbered opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All medications were applied by midwives, but residents who treat[ed] the birth and the third stage of labour were blinded to the identity of medication. Only the midwife who applied the medication opened the envelope once to read the code and then transferred the randomisation code into another identical envelope. The identities of the placebo and active medication were also concealed from caregivers and residents who followed the patient for the next 24 hours. The randomisation code was not broken until study completion."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All medications were applied by midwives, but residents who treat[ed] the birth and the third stage of labour were blinded to the identity of medication. Only the midwife who applied the medication opened the envelope once to read the code and then transferred the randomisation code into another identical envelope. The identities of the placebo and active medication were also concealed from caregivers and residents who followed the patient for the next 24 hours. The randomisation code was not broken until study completion."

Caliskan 2002 *(Continued)*

Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by collection with a sterile steel bedpan and plastic bed linen. Gauzes and pads were also collected and weighed until 1 hour after delivery of the placenta
Incomplete outcome data (attrition bias) All outcomes	Low risk	"The study enrolled 1633 women, but the data for 27 women were excluded because of lack of predelivery (n = 13) or postpartum (n = 14, short hospital stay) haemoglobin concentrations."
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	High risk	Those who withdrew from the study after randomisation were not included in the analysis
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Caliskan 2003

Methods	4-arm active-controlled double-dummy randomised trial.
Participants	Between January 2000 and October 2000, 1800 parturients were randomised in a hospital setting in Turkey. The population comprised women of unspecified parity, either singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing caesarean section, or those with gestational age less than 32 weeks or hypersensitivity to prostaglandins
Interventions	400 mcg plus 10 IU of misoprostol plus oxytocin administered orally plus by an intravenous infusion (n = 450) versus 400 mcg of misoprostol administered orally (n = 450) versus 10 IU of oxytocin administered by an intravenous infusion (n = 450) versus 200 mcg plus 10 IU of ergometrine plus oxytocin administered intramuscularly plus by an intravenous infusion (n = 450)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, manual removal of placenta, blood loss (mL), change in Hb level, third-stage duration (min), vomiting, fever, shivering
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation was computer-generated without any blocking or stratification
Allocation concealment (selection bias)	Low risk	Investigators used sealed, consecutively-numbered opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The placebo tablets were similar in size and colour but were not identical in shape to the misoprostol tablets. To minimise this limitation, the preparation and administration of the medication were carried out by a midwife who had not been involved in the management of the patient except for drug administration. The identity of medication was concealed from the resident physicians who managed the delivery and the third stage of labor. The caregivers and residents who followed up on the patient for the next 24 hours were also blind as to which patients received placebo and which received active medication. The randomisation code was not broken until the completion of the study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The placebo tablets were similar in size and colour but were not identical in shape to the misoprostol tablets. To minimise this limitation, the preparation and administration of the medication were carried out by a midwife who had not been involved in the management of the patient except for drug administration. The identity of medication was concealed from the resident physicians who managed the delivery and the third stage of labor. The caregivers and residents who followed up on the patient for the next 24 hours were also blind as to which patients received placebo and which received active medication. The randomisation code was not broken until the completion of the study."
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by collection with a sterile steel bedpan and plastic bed linen from immediately after delivery. Gauzes and pads were also collected 1 hour

Caliskan 2003   *(Continued)*

		after delivery of the placenta and weighed
Incomplete outcome data (attrition bias) All outcomes	High risk	"The data for 226 patients were excluded because of caesarean deliveries performed after randomisation (n = 206) and the lack of predelivery (n = 6) or postpartum (n = 14, short hospital stay) haemoglobin concentrations."
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	High risk	Those who withdrew from the study after randomisation were not included in the analysis
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Carbonell 2009

Methods	2-arm active-controlled randomised trial.
Participants	Between April 2007 and October 2008, 1410 parturients were randomised in a hospital setting in Spain. The population comprised women of parity 4 or less, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing caesarean section or instrumental delivery, or those with gestational age less than 32 weeks, coagulopathy, Hb less than 80 g/L, liver or kidney disorder, grand multiparity (5 or more), hypersensitivity or any contraindication for use of prostaglandins
Interventions	400 mcg and 200 mcg plus 10 IU of misoprostol plus oxytocin administered sublingually and rectally plus intramuscularly (n = 702) versus 10 IU of oxytocin administered intramuscularly (n = 698)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, additional uterotonics, transfusion, manual removal of placenta, death, blood loss (mL), change in Hb level, third-stage duration (min), NNU admissions, nausea, vomiting, fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Random assignments were generated by computer.
Allocation concealment (selection bias)	Low risk	Investigators used sequentially-numbered, opaque, sealed envelopes prepared by people not related to the study. This process was supervised by an analyst. Every morning a secretary received the sealed envelopes for distribution and this process was monitored by someone working on the study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and care-givers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Low risk	After delivery of the baby, investigators evaluated blood loss by collection with a sterile waterproof cloth placed under the mother, to channel blood into a bottle with capacity of 2 L: the volume reading was collected once beyond the third stage of labour
Incomplete outcome data (attrition bias) All outcomes	Low risk	"3 y 7 de las mujeres aleatorizadas a los grupos I y II, respectivamente, no recibieron ningún tratamiento por incumplimiento del protocolo y, como la información correspondiente a ellas no fue registrada en ningún momento, no forman parte de este informe": 3 women in the misoprostol plus active management group, and 7 women in the active management group, were excluded from the analysis due to protocol deviations and non-availability of the information
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	High risk	Those who withdrew from the study after randomisation were not included in the analysis
Funding source	Low risk	The study was supported by the Science and Ethics Committee of the Hospital Eusebio Hernandez in Habana, Cuba in conjunc-

		tion with the Clinica Mediterranea Medica in Valencia, Spain (the institutions of the authors)

Cayan 2010

Methods	4-arm controlled randomised trial.
Participants	Between January 2005 and November 2008, 160 parturients were randomised in a hospital setting in Turkey. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at high risk for PPH, who delivered by either elective or emergency caesarean. Exclusion criteria comprised parturients with thyroid disorder, inflammatory bowel disease or other bowel diseases, previous bariatric surgery or hypersensitivity to prostaglandins
Interventions	200 mcg, 400 mcg, or 600 mcg plus 10 IU of misoprostol plus oxytocin administered rectally plus by an intravenous infusion (n = 120) versus 10 IU of oxytocin administered by an intravenous infusion (n = 40)
Outcomes	The study recorded the following outcomes: fever, shivering.
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and caregivers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Unclear risk	Methods of evaluating blood loss were not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants

Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Chaudhuri 2010

Methods	2-arm active-controlled double-dummy randomised trial.
Participants	Between 1st December 2007 and 31st May 2009, 200 parturients were randomised in a hospital setting in India. The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by either elective or emergency caesarean. Exclusion criteria comprised parturients undergoing caesarean section for cord prolapse or bradycardia, or those with cardiovascular, respiratory, liver or haematological disorders or known hypersensitivity to prostaglandins
Interventions	800 mcg of misoprostol administered rectally (n = 100) versus 40 IU of oxytocin administered by an intravenous infusion (n = 100)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, additional uterotonics, transfusion, death, blood loss (mL), change in Hb level, vomiting, fever, shivering
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using computer-generated random numbers in a 1:1 ratio
Allocation concealment (selection bias)	Low risk	The packets containing the 2 drugs were sealed and opaque, and could not be identified by the surgeons and anaesthetists
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The packets containing the 2 types of drug were sealed and opaque, and could not be identified by the surgeons and anaesthetist."

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Low risk	Investigators evaluated intraoperative blood loss by collection with a suction bottle for volumetric measurement, combined with linen savers and mops weighed before and after delivery. They added the approximate volume of the contents of the suction bottle (a) to the difference in weight between dry (b) and soaked (c) linen savers and mops (1 g equivalent to 1 mL). Amniotic fluid volume (d) was calculated by multiplying amniotic fluid index by 30 mL. Finally, intraoperative blood loss was determined by subtracting amniotic fluid volume from approximate blood loss ((a plus (c - b)) - d). Furthermore, investigators evaluated postoperative bleeding over the next 8 hours by weighing soaked pads and subtracting the dry weight
Incomplete outcome data (attrition bias) All outcomes	Low risk	"4 women in group 1 [misoprostol] and 6 women in group 2 [oxytocin] were excluded from the analysis: 4 women required conversion to general anaesthesia, 5 women had traumatic intraoperative bleeding (extension of lower segment incision or ligament hematoma), and 1 woman had placenta accreta resulting in hysterectomy."
Selective reporting (reporting bias)	Low risk	The study report matches the study protocol that was registered (CTRI 2009/091/000075)
Intention to treat analysis	High risk	Those who withdrew from the study after randomisation were not included in the analysis
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Chaudhuri 2012

Methods	2-arm active-controlled double-dummy randomised trial.
Participants	Between 1st September 2009 and 31st August 2010, 530 parturients were randomised in a hospital setting in India. The population comprised women of parity 4 or less, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing augmentation of labour, caesarean section or instrumental delivery, or those with risk factors for PPH, including BMI more than 30, grand multiparity (5 or more), polyhydramnios, fetal macrosomia, antepartum haemorrhage, prolonged labour, previous PPH, Hb less than 80 g/L, severe pre-eclampsia, asthma or coagulopathy
Interventions	400 mcg of misoprostol administered sublingually (n = 265) versus 10 IU of oxytocin administered intramuscularly (n = 265)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, additional uterotonics, transfusion, manual removal of placenta, death, blood loss (mL), change in Hb level, third-stage duration (min), nausea, vomiting, fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using a computer-generated random number sequence
Allocation concealment (selection bias)	Low risk	Investigators used pre-prepared sealed and opaque packet.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The misoprostol and placebo tablets were similar in size, shape, and colour. The ampoules of oxytocin and placebo were also similar. Selection, enrolment, and randomisation were done by the resident doctors, whereas preparation of packets and confidential record maintenance was done by the labour room nursing staff in charge."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by collection with specially designed, pre-weighed absorbent thick cotton pads with plastic lining, placed under the mother. Blood

		clots, if any, were expressed from the vagina into a polythene bag. Any episiotomy wound was repaired immediately, and the swabs used for the purpose of episiotomy were not included in blood loss assessment. If necessary, pads were replaced during the observational hour after delivery. Then the soaked pad(s) and the blood clots were weighed. "The specific gravity of blood being 1.08, the amount of blood lost in mL was approximately equal to the weight in g."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"2 women in the study group and 1 woman in the control group refused sublingual administration of the drug."
Selective reporting (reporting bias)	Low risk	The study report matches the study protocol that was registered (CTRI 2009/091/000672)
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Chaudhuri 2015

Methods	2-arm active-controlled double-dummy randomised trial.
Participants	Between 1st October 2012 and 31st December 2013, 396 parturients were randomised in a hospital setting in India. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at high risk for PPH, who delivered by emergency caesarean section. Exclusion criteria comprised parturients requiring conversion to general anaesthesia, or those with cardiovascular, hepatic, or haematological disorders or any contraindication for the use of misoprostol or oxytocin
Interventions	400 mcg plus 20 IU of misoprostol plus oxytocin administered sublingually plus by an intravenous bolus and infusion (n = 198) versus 20 IU of oxytocin administered by an intravenous bolus plus infusion (n = 198)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, additional uterotonics, transfusion, death, blood loss (mL), change in Hb level, nausea, fever, shivering

Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using a computer-generated random number sequence and blocks of size 8
Allocation concealment (selection bias)	Low risk	Assignments were contained in sealed, opaque and sequentially-numbered packets
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Randomisation and confidential record maintenance were performed by residents who were not involved in the trial, and the operation theatre midwife prepared the sealed packets and allocated and administered the drugs. Thus, clinicians, investigators, data analysts, and participants were masked to the treatment allocation."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Low risk	Investigators evaluated intraoperative blood loss from after delivery of the placenta. Blood was collected with a suction bottle, linen savers and mops: the dry weights of these materials were subtracted from the soaked weights, and the total volume of intraoperative blood loss calculated on the basis that 1 g is equivalent to 1 mL. Investigators also evaluated postoperative blood loss by weighing soaked pads
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Low risk	The study report matches the study protocol that was registered (CTRI 2013/05/003645)

Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Chhabra 2008

Methods	3-arm active-controlled randomised trial.
Participants	Between dates unspecified, 300 parturients were randomised in a hospital setting in India. The population comprised women of parity 5 or less, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing augmentation of labour, caesarean section or instrumental delivery, or those with grand multiparity (more than 5), multiple pregnancy, pregnancy-induced hypertension, antepartum haemorrhage, previous caesarean, Hb less than 80 g/L, other obstetric problems or known hypersensitivity to prostaglandins
Interventions	100 mcg or 200 mcg of misoprostol administered sublingually (n = 200) versus 200 mcg of ergometrine administered by an intravenous bolus (n = 100)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, additional uterotonics, transfusion, death, blood loss (mL), change in Hb level, third-stage duration (min), nausea, vomiting, headache, fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using random number tables.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and caregivers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.

Objective assessment of blood loss	Unclear risk	Investigators evaluated blood loss by "measuring blood and blood clots collected in sponges."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Choy 2002

Methods	2-arm active-controlled randomised trial.
Participants	Between dates unspecified, 991 parturients were randomised in a hospital setting in Hong Kong. The population comprised women of parity 3 or less, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients with medical conditions that precluded the use of ergometrine, such as pre-eclampsia, cardiac disease or conditions that required prophylactic oxytocin infusion after delivery such as grand multiparity (4 or more) or presence of uterine fibroids
Interventions	500 mcg plus 5 IU of ergometrine plus oxytocin administered intramuscularly (n = 500) versus 10 IU of oxytocin administered by an intravenous bolus (n = 491)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, manual removal of placenta, blood loss (mL), change in Hb level, nausea, vomiting, hypertension, headache
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using computer-generated random numbers

Allocation concealment (selection bias)	Low risk	Investigators used sealed consecutively-numbered opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The preparation and administration of the medication was carried out by a second mid-wife who was not involved in the management of the patient except for the drug administration. The medical attendant who delivered the baby was not informed of the type of oxytocics used."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss "by measuring the amount of blood clots and weighing the towels and swabs used."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Low risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Cook 1999

Methods	3-arm active-controlled randomised trial.
Participants	Between December 1997 and December 1998, 930 parturients were randomised in a hospital setting in Australia, Papua and China. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing elective caesarean section, or those with coagulopathy, asthma, heart disease, severe renal disease, epilepsy or hypertension
Interventions	400 mcg of misoprostol administered orally (n = 455) versus 500 mcg plus 5 IU of ergometrine plus oxytocin administered intramuscularly (n = 310) versus 10 IU of oxytocin administered intramuscularly (n = 129)

Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, blood loss (mL), change in Hb level, third-stage duration (min)
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved by a random number list in blocks of 20, with separate randomisation for each centre
Allocation concealment (selection bias)	Low risk	Investigators used sequentially-numbered sealed security (opaque) envelopes containing the appropriate drug label for each centre
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study participants and caregivers were not blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessors were not blinded to treatment allocations.
Objective assessment of blood loss	Unclear risk	Investigators evaluated blood loss by combining "estimated" and "measured" values according to the standard clinical practice of each study centre. The "estimated" blood loss was judged by the attending senior midwives and/or clinicians. The "measured" blood loss was calculated as the actual volume of blood collected in a calibrated measuring jug, combined with the difference in weight between dry and blood-stained undersheets and sanitary pads
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were not collected completely from 67 study participants: "the main reasons for exclusion prior to randomisation, and following randomisation but before treatment, were the need for caesarean section and development of hypertension, either before or during labour. Two women (1 in each group) were not included in the analysis as no record was made of the primary outcome of blood loss."

Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	High risk	Those who withdrew from the study after randomisation were not included in the analysis
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Dansereau 1999

Methods	2-arm active-controlled double-blinded randomised trial.
Participants	Between February 1992 and December 1994, 694 parturients were randomised in a hospital setting in Canada. The population comprised women of unspecified parity, either singleton or multiple pregnancy, at high risk for PPH, who delivered by elective caesarean section. Exclusion criteria comprised parturients undergoing general anaesthesia or requiring a classical uterine incision, or those with heart disease, chronic hypertension requiring treatment, liver, renal, or endocrine disorders, coagulopathy, placenta praevia or placental abruption
Interventions	100 mcg of carbetocin administered by an intravenous bolus (n = 348) versus 25 IU of oxytocin administered by an intravenous bolus plus infusion (n = 346)
Outcomes	The study recorded the following outcomes: additional uterotonics, transfusion, change in Hb level, nausea, vomiting, headache, shivering, abdominal pain
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment was allocated by a computer-generated randomisation code, stratified by centre and with use of random blocks of 2
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All physicians and nurses involved, all investigators and their staff, and all sponsor representatives were kept blinded to the treatment codes at all times."

Dansereau 1999 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Unclear risk	Methods of evaluating blood loss were not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Informed consent was obtained from 694 patients. 35 patients were withdrawn from the study before they received study drug, leaving a total of 659 patients who received [the] study drug and were included in the safety analysis." Major protocol violations
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	High risk	Those who withdrew from the study after randomisation were not included in the analysis
Funding source	High risk	The study was supported by funding from Ferring Pharmaceuticals

Dasuki 2002

Methods	2-arm active-controlled randomised trial.
Participants	Between dates unspecified, 196 parturients were randomised in a hospital setting in Indonesia. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at unspecified for PPH, who delivered by vaginal delivery. Exclusion criteria were not specified
Interventions	600 mcg of misoprostol administered orally (n = 98) versus 10 IU of oxytocin administered intramuscularly (n = 98)
Outcomes	The study recorded the following outcomes: blood loss (mL), third-stage duration (min), shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.

Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and caregivers) was unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Unclear risk	Methods of evaluating blood loss were not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

de Groot 1996b

Methods	3-arm placebo-controlled randomised trial.
Participants	Between July 1993 and July 1994, 371 parturients were randomised in a hospital and community setting in the Netherlands. The population comprised women of unspecified parity, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing induction or augmentation of labour or instrumental delivery, requiring tocolysis or those who refuse to take part or with cardiac disease, multiple pregnancy, non-cephalic presentation, polyhydramnios, coagulopathy, stillbirth, antepartum haemorrhage, Hb less than 4.8 mmol/L or previous complication in third stage
Interventions	Placebo or control (n = 143) versus 5 IU of oxytocin administered intramuscularly (n = 78). There were 4 exclusions post randomisation but it was unclear from which group. The oral ergometrine group was merged with the control group for analysis
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, manual removal of placenta, death, blood loss (mL)

Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using a computer-generated random list
Allocation concealment (selection bias)	Low risk	Investigators used identical study boxes. Care was taken that no difference could be seen or heard between the packages of the ergometrine/placebo tablets and the oxytocin ampoules
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was "double-blind" with placebo to match ergometrine treatment, but "to allow comparison with a standard prophylactic regimen a third group receiving the standard intramuscular oxytocin was added, but for obvious reasons this could not be conducted in a blind manner."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by collection with a "fresh" perineal pad placed under the mother from immediately after birth until 1 hour after the delivery of the placenta. The difference in the weight of the pad before and after delivery was calculated on the basis that 1 g is equivalent to 1 mL of blood. "During delivery some blood was usually spattered on the drapes and gowns of the attendants, although attempts were made to minimise such losses. This gave a constant error of approximately 10%. In addition, the placental interstices contain maternal blood (about 9% of placental weight). As systematic overestimations (amniotic fluid) and underestimations (blood loss) are likely to be equally distributed among the groups, no corrections have been made for them."

Incomplete outcome data (attrition bias) All outcomes	Low risk	"4 women with exclusion criteria were entered erroneously (3 forcipal extractions, 1 augmentation). They are considered as non-participants."
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	High risk	Those who withdrew from the study after randomisation were not included in the analysis
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Derman 2006

Methods	2-arm placebo-controlled randomised trial.
Participants	Between September 2002 and December 2005, 1620 parturients were randomised in a community setting in India. The population comprised women of unspecified parity, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients at high risk and inappropriate for home or community births according to India's ministry of health guidelines including those undergoing elective caesarean section or breech vaginal delivery, or those previous caesarean section, Hb less than 80 g/L, antepartum haemorrhage, hypertension, multiple pregnancy, history of previous antepartum or PPH, retained placenta, uterine inversion, diabetes, heart disease, seizures, placenta praevia, asthma or contraindications to misoprostol
Interventions	600 mcg of misoprostol administered orally (n = 812) versus placebo or control (n = 808)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, additional uterotonics, transfusion, manual removal of placenta, death, blood loss (mL), nausea, vomiting, fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using a randomisation list with a random block size generated by the data co-ordinating centre and stratified by the midwife

Allocation concealment (selection bias)	Low risk	The envelopes were numbered and each envelope had a 5-digit code number assigned to it. The first 2 digits were the auxiliary nurse midwife number, followed by a sequence number beginning with 001 and ending with 100, assigned to the individual participant. Non-distinguishable envelopes in batches of 100 were distributed to each of the midwives affiliated with the 4 selected primary-health centres
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The identical placebo was specifically manufactured for the study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by collection with a polyurethane blood collection drape placed under the mother from immediately after birth until 1 hour after delivery of the baby. The blood collection drape included a calibrated receptacle specifically developed for the study. In the event of persistent bleeding beyond 1 hour, the drape was removed at 1 hour, blood loss measured, and a new drape used with a second measurement made at 2 hours
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Low risk	The study report matches the study protocol that was registered (ClinicalTrials.gov NCT00097123)
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by funding from the National Institute of Child Health and Human Development (public funding) and the Bill and Melinda Gates Foundation (public funding)

Dhananjaya 2014

Methods	2-arm active-controlled randomised trial.
Participants	Between December 2011 and May 2013, 100 parturients were randomised in a hospital setting in India. The population comprised women of parity 4 or less, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients with grand multiparity (not defined), rhesus negative blood group, cardiac disease, diabetes, bleeding disorder, precipitated labour, overdistended uterus, traumatic PPH, PROM/chorioamnionitis, intrauterine death, previous caesarean section/scar on uterus or inability to obtain the informed consent
Interventions	10 IU of oxytocin administered intramuscularly (n = 50) versus 200 mcg of ergometrine administered intramuscularly (n = 50)
Outcomes	The study recorded the following outcomes: PPH at 500, additional uterotonics, transfusion, blood loss (mL), change in Hb level, third-stage duration (min), nausea, vomiting, headache
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Investigators used a systematic random sampling method.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and caregivers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by collection with drapes that were weighed together with mops and clots, and by measurement of Hb concentration and haematocrit of a sample of venous blood before delivery and 24 hours after birth. A sample of venous blood before delivery and 24 hours after the birth was also collected, for Hb and haematocrit measurement "as an objective index of blood loss."

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Docherty 1981

Methods	2-arm active-controlled randomised trial.
Participants	Between dates unspecified, 50 parturients were randomised in a hospital setting in the UK. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at unspecified for PPH, who delivered by vaginal delivery. Exclusion criteria were not specified
Interventions	10 IU of oxytocin administered intramuscularly (n = 25) versus 500 mcg plus 5 IU of ergometrine plus oxytocin administered intramuscularly (n = 25)
Outcomes	The study recorded the following outcome: Blood loss (mL).
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and caregivers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.

Objective assessment of blood loss	Unclear risk	Methods of evaluating blood loss were not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Eftekhari 2009

Methods	2-arm active-controlled randomised trial.
Participants	Between the beginning of August 2007 and the end of December 2007, 100 parturients were randomised in a hospital setting in Iran. The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by elective caesarean section. Exclusion criteria comprised parturients with multiple pregnancy, prolonged labour more than 12 h, 2 or more previous caesarean sections, previous uterine rupture, Hb less than 80 g/L, who had a history of heart, renal or liver disorders or had a coagulopathy
Interventions	400 mcg of misoprostol administered sublingually (n = 50) versus 20 IU of oxytocin administered by an intravenous infusion (n = 50)
Outcomes	The study recorded the following outcomes: additional uterotonics, blood loss (mL), change in Hb level
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	By a simple randomisation method, patients were allocated into 2 equal groups
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.

Eftekhari 2009 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Study participants and caregivers were not blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by collection in a suction bottle, and with drapes and pads beneath the mother. Amniotic fluid was suctioned and measured, and then subtracted from the total volume of the suction bottle. Meanwhile the known dry weight(s) of drapes and pads were subtracted from the soaked weights of these materials. Measurements of blood collected in the suction bottle and on drapes and pads were added together
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data
Selective reporting (reporting bias)	High risk	The protocol of the study was unavailable for verification, but not all of the outcomes projected by methodological descriptions were reported as results in the study report (cases of transfusion were omitted)
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

El Behery 2015

Methods	2-arm active-controlled double-dummy randomised trial.
Participants	Between 1st January 2013 and 31st June 2014, 180 parturients were randomised in a hospital setting in Egypt. The population comprised nulliparous women with a singleton pregnancy, at high risk for PPH, who delivered by emergency caesarean section. Exclusion criteria comprised parturients undergoing elective caesarean section, vaginal delivery or general anaesthesia, or those who were multigravida, or with malpresentation, fetal anomalies, placenta praevia, diabetes, hypertension, pre-eclampsia or cardiac disease

Interventions	100 mcg of carbetocin administered by an intravenous bolus (n = 90) versus 20 IU of oxytocin administered by an intravenous infusion (n = 90)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, additional uterotonics, transfusion, death, blood loss (mL), change in Hb level, nausea, headache, fever
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation was computer-generated.
Allocation concealment (selection bias)	Low risk	Investigators used sealed, opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was "double-blinded": "a double dummy system for administration was used."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss "in the usual way (visual estimation, number of used swabs and amount of aspirated blood) ."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"100 cases were excluded (4 had congenital fetal anomalies, 7 cases had placenta praevia, 5 cases were diabetic, 8 had hypertension, 9 had pre-eclampsia, 3 cases were cardiac, 28 cases [required] general anaesthesia, 17 cases delivered vaginally and 19 delivered by elective caesarean section)."
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were

El Behery 2015 (*Continued*)

		randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

El Tahan 2012

Methods	2-arm placebo-controlled randomised trial.
Participants	Between dates unspecified, 382 parturients were randomised in a hospital setting in Egypt. The population comprised women of parity 3 or less, a singleton pregnancy, at high risk for PPH, who delivered by elective caesarean section. Exclusion criteria comprised parturients with asthma, anaemia, bleeding disorders, cardiac disease, inflammatory disease, bowel disease, multiple pregnancy, pre-eclampsia, placenta praevia, placental abruption, previous APH, previous PPH, grand multiparity (not defined), fibroids, growth restriction, fetal malformations or allergy to prostaglandins
Interventions	400 mcg plus 10 IU of misoprostol plus oxytocin administered sublingually plus by an intravenous bolus (n = 191) versus 10 IU of oxytocin administered by an intravenous infusion (n = 191)
Outcomes	The study recorded the following outcomes: morbidity, additional uterotonics, transfusion, death, blood loss (mL), vomiting, fever, shivering, abdominal pain
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation code was computer-generated.
Allocation concealment (selection bias)	Low risk	Investigators used sequentially-numbered sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo and misoprostol tables "looked identical in size, colour, and packing."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	High risk	Investigators evaluated intraoperative blood loss by collection in a suction bottle minus sonographically estimated amniotic

		fluid volume, together with visual estimates of the volume of blood on the floor and the weight differences between dry and used towels, linens, and swabs. Visual estimates were performed by obstetricians blinded to treatment allocation. Towels, linen and swabs were weighed with an electronic scale. Weights were added to volumetric values on the basis that 1 g is equivalent to 1 mL. Investigators evaluated postoperative blood loss by weighing bed linen, gowns and perineal pads. Furthermore, blinded investigators estimated blood loss by multiplying maternal blood volume in mL by the difference between preoperative and postoperative haematocrit measurements, all divided by preoperative haematocrit measurements
Incomplete outcome data (attrition bias) All outcomes	Low risk	"4 patients in the placebo group and 12 patients in the misoprostol group were excluded from the study due to loss to follow-up or missed preoperative hematocrit data."
Selective reporting (reporting bias)	Unclear risk	The study report matches the study protocol that was registered retrospectively (ClinicalTrials.gov NCT01466530)
Intention to treat analysis	High risk	Those who withdrew from the study after randomisation were not included in the analysis
Funding source	Low risk	The study was supported by funding from Mansoura University (the institution of the authors)

El-Refaey 2000

Methods	2-arm active-controlled randomised trial.
Participants	Between April 1996 and March 1998, 1000 parturients were randomised in a hospital setting in the UK. The population comprised women of unspecified parity, either singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing caesarean section or water birth, or those with severe asthma
Interventions	500 mcg of misoprostol administered orally (n = 501) versus 500 mcg plus 5 IU of ergometrine plus oxytocin administered intramuscularly (n = 499)

Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, manual removal of placenta. death, blood loss (mL), change in Hb level, third-stage duration (min), nausea, vomiting, headache, fever, shivering, abdominal pain
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Statistician using computer-generated block randomisation with varying block size
Allocation concealment (selection bias)	Low risk	Investigators used opaque, sequentially-numbered sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study participants and caregivers were not blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessors were not blinded to treatment allocations.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss by the estimation of attending physicians
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Elgafor 2013

Methods	2-arm active-controlled double-dummy randomised trial.
Participants	Between February 2010 and October 2012, 380 parturients were randomised in a hospital setting in Egypt. The population comprised women of unspecified parity, either singleton or multiple pregnancy, at high risk for PPH, who delivered by elective caesarean section. Exclusion criteria comprised parturients undergoing general anaesthesia, or those with coagulopathy, coronary artery disease, hypertension, PPH due to causes other than uterine atony or hypersensitivity to carbetocin
Interventions	400 mcg plus 20 IU of misoprostol plus oxytocin administered sublingually plus by an intravenous infusion (n = 190) versus 100 mcg of carbetocin administered by an intravenous bolus (n = 190)
Outcomes	The study recorded the following outcomes: morbidity, additional uterotonics, transfusion, death, blood loss (mL), change in Hb level, nausea, vomiting, headache, hypotension, fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using a computer-generated random number sequence
Allocation concealment (selection bias)	Low risk	Drugs were in pre-prepared sealed and opaque packets.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Randomisation was done by the resident doctors immediately before transfer to theatre, whereas preparation of packets and confidential record maintenance was done by the labour room nursing staff... Caesarean delivery was performed by 4 senior obstetricians who were blinded to the allocation."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss "in the usual way (visual estimation, number of used swabs and amount of aspirated blood) ."

Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Elsedeek 2012

Methods	2-arm placebo-controlled randomised trial.
Participants	Between 1st January 2008 and 1st January 2009, 400 parturients were randomised in a hospital setting in Egypt. The population comprised women of parity 4 or less, a singleton pregnancy, at high risk for PPH, who delivered by elective caesarean section. Exclusion criteria comprised parturients undergoing their first elective caesarean section, or those unsure of gestation or with hypertension, diabetes, oligohydramnios, abnormal placenta or abnormal laboratory investigations
Interventions	400 mcg plus 10 IU of misoprostol plus oxytocin administered rectally plus by an intravenous infusion (n = 200) versus 10 IU of oxytocin administered by an intravenous infusion (n = 200)
Outcomes	The study recorded the following outcomes: PPH at 1000, additional uterotonics, transfusion, blood loss (mL), change in Hb level, NNU admissions, fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using computer-generated tables.
Allocation concealment (selection bias)	Unclear risk	Allocation was placed in sealed envelopes until the time of operation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Attending obstetricians and other caregivers were blinded to treatment allocations

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss from after uterine incision, by collection in 2 separate suction sets administered by a nurse, and by weighing surgical towels before and after each operation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The study protocol was registered retrospectively (ACTRN 12611000638932)
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by funding from the institution of the authors, or conducted without external funding

Enakpene 2007

Methods	2-arm active-controlled randomised trial.
Participants	Between 4th January 2004 and 30th January 2005, 864 parturients were randomised in a hospital setting in Nigeria. The population comprised women of unspecified parity, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients with pre-eclampsia, hypertension, cardiac disease, severe anaemia, asthma, renal/hepatic disorders, grand multiparity (not defined), multiple pregnancy, polyhydramnios, previous PPH, fibroids or contraindications to misoprostol or ergometrine
Interventions	400 mcg of misoprostol administered orally (n = 432) versus 500 mcg of ergometrine administered intramuscularly (n = 432)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, additional uterotonics, manual removal of placenta, death, blood loss (mL), change in Hb level, third-stage duration (min), nausea, vomiting, headache, fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was by simple random selection. An independent statistician generated sets of 4 random letters, which were in boxes, and each box contained 4 separate random allocations which was equivalent to an opaque sealed envelope stratified in a block of 4
Allocation concealment (selection bias)	Low risk	Investigators used opaque sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study was "single-blinded." The identity of those blinded was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss by a combination of careful collection in a receptacle after the delivery of the baby, by visual estimation of blood loss, and by extrapolation of blood loss using the weight difference of the total perineal pad used up to 24 hours postpartum
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification, but not all of the outcomes projected by methodological descriptions were reported as results in the study report (cases of transfusion, chest pain and abdominal pain were omitted)
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by funding from the National Postgraduate Medical College and Faculty of Obstetrics and Gynaecology of the University College Hospital in

	Ibadan, Nigeria (the institution of the authors)

Ezeama 2014

Methods	2-arm active-controlled double-dummy randomised trial.
Participants	Between 1st September 2011 and 31st May 2012, 300 parturients were randomised in a hospital setting in Nigeria. The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing caesarean section, or those with premature labour (less than 28 weeks), multiple pregnancy, antepartum haemorrhage, hypertension in pregnancy, severe anaemia or haemoglobinopathy
Interventions	10 IU of oxytocin administered intramuscularly (n = 151) versus 500 mcg of ergometrine administered intramuscularly (n = 149)
Outcomes	The study recorded the following outcomes: PPH at 500, additional uterotonics, transfusion, manual removal of placenta, blood loss (mL), third-stage duration (min), nausea, vomiting, hypertension, headache
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using computer-generated random tables
Allocation concealment (selection bias)	Low risk	A person uninvolved with the study prepared the study drugs. The labels on the ampoules (which were similar in size and colour) were removed and the ampoules were placed in opaque sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"A person uninvolved with the study prepared the study drugs… The labels on the ampoules (which were similar in size and colour) were removed and the ampoules were placed in opaque sealed envelopes, such that only the computer-generated randomisation numbers on the envelopes were available to identify the study drug during unblinding."

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by collection with "a fresh large perineal pad with plastic backing." They placed all the gauzes and perineal pads used to absorb the blood into a polythene bag, and subtracted the dry weight from the wet weight. Volume of blood loss was calculated on the basis that 1 g is equivalent to 1 mL
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Low risk	The study protocol was registered (PACTR 201105000292708).
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by funding from the institution of the authors

Fararjeh 2003

Methods	2-arm active-controlled randomised trial.
Participants	Between 1st January 2002 and 30th June 2002, 97 parturients were randomised in a hospital setting in Turkey. The population comprised women of parity 4 or less, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing elective caesarean section or instrumental delivery, or those with premature labour (less than 37 weeks), postmaturity (more than 43 weeks), grand multiparity (more than 4), twin pregnancy, growth restriction, macrosomia, Hb less than 100 g/L, systemic disorder, prolonged third stage, manual removal of placenta or additional lacerations due to episiotomy or where it took longer than 30 min to repair lacerations after episiotomy
Interventions	400 mcg of misoprostol administered rectally (n = 49) versus 200 mcg plus 10 IU of ergometrine plus oxytocin administered intramuscularly (n = 48)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, blood loss (mL) , change in Hb level

Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was achieved using block randomisation.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and care-givers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by collection with scale vessels, and by subtraction of the dry weight(s) of cloths and pads from the soaked weight(s) of these items
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Fawole 2011

Methods	2-arm placebo-controlled randomised trial
Participants	1345 parturients were randomised in a hospital setting in Nigeria. The population comprised multiparous women, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered vaginally. Exclusion criteria comprised severe allergic conditions or asthma, age below 18 years, pyrexia above 38°C, or abortion of the pregnancy

Interventions	400 mcg of misoprostol administered sublingually plus 10 IU of oxytocin or 250 mcg to 500 mcg of ergometrine administered intramuscularly or by an intravenous bolus (n = 658) or intravenous bolus versus 10 IU of Oxytocin or 250 mcg to 500 mcg of ergometrine administered intramuscularly or intravenously (n = 660)
Outcomes	Could not include in the analysis as could not separate out the patients that received oxytocin from those who received ergometrine
Notes	Contact with study authors for additional information: Yes. Additional data from authors: Yes, but data not provided separate for each drug used and could not be included in the meta-analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment was allocated in blocks of 6-8 women by the research nurse, who used a computer-generated randomisation sequence
Allocation concealment (selection bias)	Low risk	The trial drugs were concealed in sealed, sequentially numbered opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was identical in shape, colour, size, and design.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded.
Objective assessment of blood loss	Low risk	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
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses stated by authors but 27 women randomised were not included in the analysis for the primary outcome
Selective reporting (reporting bias)	Unclear risk	No available protocol.

Fawole 2011 *(Continued)*

Intention to treat analysis	Unclear risk	27 women randomised were not included in the analysis for the primary outcome
Funding source	Low risk	The trial was funded by theMedical Research Council of South Africa

Fazel 2013

Methods	2-arm active-controlled randomised trial.
Participants	Between dates unspecified in 2009, 100 parturients were randomised in a hospital setting in Iran. The population comprised women of parity 3 or less, a singleton pregnancy, at high risk for PPH, who delivered by elective caesarean section. Exclusion criteria comprised parturients with twin pregnancy, fetal distress, pregnancy-induced hypertension, oligohydramnios, polyhydramnios, macrosomia, grand multiparity (4 or more), HELLP syndrome, coagulopathy, asthma, heart/lung/liver disease, previous more than 1 caesarean section, previous myomectomy, previous other abdominal operations, febrile diseases or sensitivity to prostaglandins
Interventions	400 mcg of misoprostol administered rectally (n = 50) versus 10 IU of oxytocin administered by an intravenous infusion (n = 50)
Outcomes	The study recorded the following outcomes: transfusion, blood loss (mL), nausea, vomiting, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Investigators used a table of random numbers.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and caregivers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	High risk	Investigators evaluated intraoperative blood loss by collection with an isolated suction. The volume of blood collected in suction

		was combined with the volume of blood collected in gauzes and gowns: every small gauze soaked with blood was considered to contain 20 mL, and every large gauze soaked with blood 50 mL, and every g increase in the weight of a gown was considered as equivalent to 1 mL of blood
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by funding from the Kashan University of Medical Sciences (the institution of the authors)

Fekih 2009

Methods	2-arm active-controlled randomised trial.
Participants	Between 1st March 2007 and 1st June 2007, 250 parturients were randomised in a hospital setting in Tunisia. The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by either elective or emergency caesarean. Exclusion criteria comprised parturients undergoing caesarean section with general anaesthesia, or those with placenta praevia, retroplacental clot, multiple pregnancy, premature labour (less than 32 weeks), intra-uterine death, Hb less than 80 g/L, coagulopathy, HELLP syndrome, antepartum haemorrhage, ruptured uterus, previous more than 2 caesareans or other uterine scar, prolonged labour (more than 12 hours) or pyrexia
Interventions	200 mcg plus 20 IU of misoprostol plus oxytocin administered sublingually plus by an intravenous bolus and infusion (n = 125) versus 20 IU of oxytocin administered by an intravenous bolus plus infusion (n = 125)
Outcomes	The study recorded the following outcomes: PPH at 1000, transfusion, blood loss (mL) , change in Hb level, nausea, vomiting, headache, fever, shivering
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation was computer-generated.
Allocation concealment (selection bias)	Low risk	A slip of paper was placed inside an opaque, sealed envelope
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and caregivers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	High risk	Investigators evaluated perioperative blood loss as a combination of the volume of liquid in the suction collection jar, and the weight of swabs and pads
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Fenix 2012

Methods	2-arm active-controlled double-dummy randomised trial.
Participants	Between May 2011 and August 2011, 75 parturients were randomised in a hospital setting in the Philippines. The population comprised women of unspecified parity, either singleton or multiple pregnancy, at high risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients with pre-existing hypertension, pre-eclampsia, diabetes, asthma, cardiac/renal diseases, coagulopathy, abnormal laboratory tests or allergy to the study medication
Interventions	100 mcg of carbetocin administered by an intravenous bolus (n = 39) versus 10 IU of oxytocin administered by an intravenous infusion (n = 36)

Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional utero-tonics. transfusion, blood loss (mL,. change in Hb level, nausea, vomiting, headache, tachycardia, abdominal pain
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation was computer-generated.
Allocation concealment (selection bias)	Unclear risk	Investigators used sealed, consecutively-numbered envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The patient and the principal investigator attending the delivery were blinded to the type of medication administered" [additional information from the authors]
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"In addition to these, the following were recorded by assigned personnel not blinded in this study: any adverse events or experiences from the 2 groups (carbetocin versus oxytocin); vital signs before and after drug infusion, the need for an additional uterotonic in each group, the need for a uterine massage and the intensity of the uterine contraction after infusion of the assigned drug."
Objective assessment of blood loss	High risk	Investigators evaluated blood loss by visual estimation, not including blood loss considered to result from repair of lacerations
Incomplete outcome data (attrition bias) All outcomes	High risk	"9 women in the carbetocin group and 6 women in the oxytocin group failed to have a paired haemoglobin test to measure the change in haemoglobin 24 hours after delivery because they refused further blood extraction. These 15 women were excluded."
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.

Intention to treat analysis	High risk	Not all study participants were included in the analysis.
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Fu 2003

Methods	2-arm controlled randomised trial.
Participants	Between October 2002 and April 2003, 156 parturients were randomised in a hospital setting in China. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria were not specified
Interventions	400 mcg of misoprostol administered orally (n = 80) versus placebo or control (n = 76)
Outcomes	The study recorded the following outcomes: PPH at 500, blood loss (mL)
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and caregivers) was unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss in the 2 hours after delivery and after all amniotic fluids had been drained, by collection in a small tray and absorption into disposable, sterile, water-resistant gauze. The contents were weighed and volume was determined on the basis that 1.05 g is equivalent to 1 mL of blood. A measuring cup was used to estimate the blood in the tray; blood that soaked into the gauze was measured on the basis that material

		measuring 10 cm by 10 cm holds 10 mL of blood. These 3 measurements were combined to ascertain total blood loss
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Garg 2005

Methods	2-arm active-controlled randomised trial.
Participants	Between 2002 and 2003, 200 parturients were randomised in a hospital setting in India. The population comprised women of primigravidas, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria were not specified
Interventions	600 mcg of misoprostol administered orally (n = 100) versus 200 mcg of ergometrine administered by an intravenous bolus (n = 100)
Outcomes	The study recorded the following outcomes: PPH at 500, additional uterotonics, manual removal of placenta, third-stage duration (min), nausea, vomiting, headache, fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomised in 1:1 ratio by random number sequence
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and care-givers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Unclear risk	Methods of evaluating blood loss were not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Gavilanes 2016

Methods	2-arm active-controlled randomised trial.
Participants	Between dates unspecified, 100 parturients were randomised in a hospital setting in Ecuador. The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by elective caesarean section. Exclusion criteria comprised parturients with Hb less than 80 g/L, multiple pregnancy, polyhydramnios, previous uterine rupture, bleeding disorders, intrauterine death or hyperthermia (more than 38.5°C)
Interventions	400 mcg of misoprostol administered sublingually (n = 50) versus 10 IU of oxytocin administered by an intravenous infusion (n = 50)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, blood loss (mL), nausea, vomiting, headache, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation was computer-generated.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study participants and caregivers were not blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Low risk	Investigators evaluated postoperative blood loss by collection with "suction apparatus and sterile drapes before irrigation" and by weighing the blood collected in abdominal swabs and gauzes with a calibrated scale (Zhongshan Camry Electronic Co Ltd, model EK 4052-E, Guangdong, China). Investigators estimated the volume of blood loss "by subtraction of amniotic fluid at 30 cc per each centimetre reported by amniotic fluid index."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Gerstenfeld 2001

Methods	2-arm placebo-controlled randomised trial.
Participants	Between dates unspecified, 400 parturients were randomised in a hospital setting in the USA. The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients with multiple pregnancy, coagulopathy, Hb less than 70 g/L, indication for caesarean section or contraindication to prostaglandin or oxytocin use
Interventions	400 mcg of misoprostol administered rectally (n = 201) versus 20 IU of oxytocin administered by an intravenous infusion (n = 199)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, nausea, vomiting, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by an uninvolved party and determined by a random number sequence
Allocation concealment (selection bias)	Low risk	The random number sequence was prepared by a third party and was concealed until the patient was enrolled. Packets were prepared in advance of randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The random number sequence was "concealed until the patient was enrolled" and "packets were prepared in advance of randomisation."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss (a) by collection with drapes placed under the mother. Each drape included a plastic pouch and measured volume in mL. Meanwhile the dry weights of delivery linen and sponges were subtracted from bloodied weights to determine the volume of blood collected with these materials, on the basis that 1 g is equivalent to 1 mL. The volumes of blood in drapes and linen were

		added together. Furthermore "if amniotic fluid loss [after placement of the drape] was significant… the approximate percentage was recorded on the data sheet and blood loss was adjusted accordingly." Investigators evaluated blood loss (b) by estimation of the delivery attendant(s). Investigators evaluated blood loss (c) by measurement of Hb and haematocrit values were obtained on admission and on postpartum day 1. The differences between these 2 values were recorded
Incomplete outcome data (attrition bias) All outcomes	High risk	"Of the 75 women who were excluded from analysis, 73 underwent caesarean deliveries, 1 woman was discharged to home before delivery, and 1 had an initial Hb of 6.8 mg/dL."
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	High risk	Those who withdrew from the study after randomisation were not included in the analysis
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Gulmezoglu 2001

Methods	2-arm active-controlled double-blinded randomised trial.
Participants	Between April 1998 and November 1999, 18530 parturients were randomised in a hospital setting in Argentina, China, Egypt, Ireland, Nigeria, South Africa, Switzerland, Thailand, and Vietnam. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing elective or emergency caesarean section after randomisation, or those with asthma, severe chronic allergic conditions, abortion, pyrexia (more than 38°C) or inability to give consent
Interventions	600 mcg of misoprostol administered orally (n = 9264) versus 10 IU of oxytocin administered intramuscularly or by an intravenous bolus (n = 9266)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, additional uterotonics, transfusion, manual removal of placenta, death, blood loss (mL), third-stage duration (min, nausea, vomiting, fever, shivering

Gulmezoglu 2001 *(Continued)*

| Notes | Contact with study authors for additional information: yes. Additional data from authors: yes |

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The random allocation schedule was generated centrally at WHO, Geneva, Switzerland, by computer-generated random numbers and was stratified by country. Within the strata, women were individually randomised into 1 of 2 intervention groups with randomly varying block sizes of 4-6 women
Allocation concealment (selection bias)	Low risk	The treatment packs were sealed, numbered sequentially, and could only be taken from the dispenser consecutively
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The treatment packs and their contents were identical in shape, colour, weight, and feel… Double-blinding, including double placebos, ensured that ascertainment bias in the measurement of blood loss and use of additional uterotonics was unlikely. However, unblinding could have occurred because of the higher rate of shivering associated with misoprostol."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss from the time of delivery of the baby until the third stage of the labour was completed, when the mother was transferred to postnatal care (usually up to 1 hour postpartum). Immediately after the cord was clamped and cut, they passed a flat bedpan or an unsoiled receiver under the mother. The collected blood was poured into a standard measuring jar provided by WHO for volumetric measurement. "To simplify the procedure... small gauze swabs soaked with blood were put into the measuring jar and included in

Gulmezoglu 2001 *(Continued)*

		the measurement together with the blood and clots."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Investigators excluded "37 and 34 women with emergency caesarean section, and 13 and 4 women lost to follow-up in miso-prostol and oxytocin groups, respectively, for blood loss at least 1000 mL, and 2 and 4 women without information on the need for additional uterotonics."
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	High risk	Not all study participants were included in the analysis.
Funding source	Low risk	The study was supported by funding from the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training. Searle (Skokie, IL, USA) and Novartis (Basel, Switzerland) donated the active and placebo medications used in the trial

Gupta 2006

Methods	2-arm active-controlled double-blinded randomised trial.
Participants	Between dates unspecified, 200 parturients were randomised in a hospital setting in India. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria were not specified
Interventions	600 mcg of misoprostol administered rectally (n = 100) versus 10 IU of oxytocin administered intramuscularly (n = 100)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, manual removal of placenta, blood loss (mL). change in Hb level, third-stage duration (min), nausea, fever, shivering
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Randomisation was achieved using computer-generated random tables
Allocation concealment (selection bias)	Unclear risk	A sealed envelope with a code number was opened when vaginal delivery was imminent. The code was not broken till the end of the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was "double-blind." "Each envelope contained either 3 tablets of 200 mcg misoprostol and an ampoule of normal saline or 3 identical looking placebo tablets and an ampoule of 10 IU oxytocin."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by collection with a BRASS-V calibrated drape placed under the mother. Pre-weighed gauzes were used to clean any perineal tears or episiotomy. After 1 hour the dry weight of the sponges was subtracted from the soiled weight, and added to the volume of blood collected in the drape on the basis that 1 g is equivalent to 1 mL
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Hamm 2005

Methods	2-arm placebo-controlled randomised trial.
Participants	Between August 2000 and May 2004, 352 parturients were randomised in a hospital setting in the USA. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at high risk for PPH, who delivered by either elective or emergency caesarean. Exclusion criteria were not specified
Interventions	200 mcg plus 20 IU of misoprostol plus oxytocin administered sublingually plus by an intravenous infusion (n = 173) versus 20 IU of oxytocin administered by an intravenous infusion (n = 179)
Outcomes	The study recorded the following outcomes: PPH at 1000, additional uterotonics, transfusion, blood loss (mL), change in Hb level
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Low risk	The group assignments were available only to the pharmacy. The nurse selected an opaque vial from the drug cabinet that contained either a 200 mg misoprostol tablet or placebo. The vial number (which had been assigned in the pharmacy) and patient identification were sent to the pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study participants and caregivers were blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Unclear risk	Methods of evaluating blood loss were not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.

| Intention to treat analysis | Low risk | All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised |
| Funding source | Unclear risk | Source(s) of funding for the study were unclear. |

Harriott 2009

Methods	2-arm active-controlled randomised trial.
Participants	Over 6 months between dates unspecified, 140 parturients were randomised in a hospital setting in West Indies. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients with previous PPH, hypertension, previous caesarean, intrauterine death, sepsis/pyrexia (more than 38°C), antepartum haemorrhage or Hb less than 80 g/L
Interventions	500 mcg plus 5 IU of ergometrine plus oxytocin administered intramuscularly (n = 70) versus 400 mcg of misoprostol administered rectally (n = 70)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, manual removal of placenta, death, blood loss (mL), change in Hb level, third-stage duration (min), nausea, vomiting, hypertension, fever, shivering
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated block randomisation was used to randomly assign participants
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Both the patient and the midwife conducting the delivery were aware of the drug administered."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessors were not blinded to treatment allocations.

Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by collection with a modified plastic drape placed under the mother from the commencement of the third stage of labour, until 1 hour after delivery. The collection drape measured 168 cm by 84 cm, and contained folded over side-wings (to act as a chute) and a 34-cm collection pouch made by folding the distal end of the drape. Standard sterile drapes were placed above the blood collection drape. Every effort was made to avoid soiling the sterile drapes before delivery of the baby, because they were not weighed. After delivery, overlying sterile drapes were removed to facilitate the use of the collection drape
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by funding from the Mona Campus and Research Publication Committee of the University of the West Indies (the institution of the authors)

Hofmeyr 1998

Methods	2-arm placebo-controlled randomised trial.
Participants	Between dates unspecified, 500 parturients were randomised in a hospital setting in South Africa. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing augmentation of labour, or those with hypertension, diabetes or previous caesarean
Interventions	400 mcg of misoprostol administered orally (n = 250) versus placebo or control (n = 250)
Outcomes	The study recorded the following outcomes: PPH at 1000, additional uterotonics, transfusion, manual removal of placenta, shivering, abdominal pain

Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using a computer-generated random sequence, in balanced blocks of 8
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"The tablets were either misoprostol 2 x 200 mcg or 2 placebo tablets similar in size and colour but not shape. Efforts to obtain identical placebo tablets were unsuccessful. This method of blinding proved to be effective. In only 1 case did the attending midwife inadvertently catch sight of the tablets."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Low risk	Within a minute of delivery, investigators removed any linen soiled with amniotic fluid, and placed a fresh, disposable absorbent linen-saver sheet with plastic backing, and a low wedge-shaped plastic "fracture" bedpan under the mother. "This was found to be a comfortable and efficient way of collecting the great majority of blood lost after delivery, and could be left in place without discomfort even during perineal suturing. When active bleeding had stopped, any blood clots were expressed from the uterus, the bedpan was removed and a sanitary towel was applied. The [volume of] blood in the bedpan was measured in a measuring jug. An hour after delivery, any bloodstained linen-savers and sanitary towels were placed in a plastic bag and weighed in g." After subtracting the known dry weights of these materials, the bloodstained weights were added to the volume of blood collected in the bedpan to ascer-

Hofmeyr 1998 *(Continued)*

		tain the total blood loss in the first hour after delivery
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by funding from the South African Medical Research Council (public funding)

Hofmeyr 2001

Methods	2-arm placebo-controlled randomised trial.
Participants	Between dates unspecified, 600 parturients were randomised in a hospital setting in South Africa. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at unspecified for PPH, who delivered by vaginal delivery. Exclusion criteria were not specified
Interventions	600 mcg of misoprostol administered orally (n = 300) versus placebo or control (n = 300)
Outcomes	The study recorded the following outcomes: PPH at 1000, additional uterotonics, transfusion, manual removal of placenta, nausea, vomiting, fever, shivering, abdominal pain
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random assignments were generated by computer in blocks of 18
Allocation concealment (selection bias)	Low risk	Investigators used sequentially-numbered, opaque test tubes.

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Misoprostol and placebo were similar in size and colour but not shape
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Low risk	Within a minute of delivery, investigators removed any linen soiled with amniotic fluid, and placed a fresh, disposable absorbent linen-saver sheet with plastic backing, and a low wedge-shaped plastic "fracture" bedpan under the mother. "This was found to be a comfortable and efficient way of collecting the great majority of blood lost after delivery, and could be left in place without discomfort even during perineal suturing. When active bleeding had stopped, any blood clots were expressed from the uterus, the bedpan was removed and a sanitary towel was applied. The [volume of] blood in the bedpan was measured in a measuring jug. An hour after delivery, any bloodstained linen-savers and sanitary towels were placed in a plastic bag and weighed in g." After subtracting the known dry weights of these materials, the bloodstained weights were added to the volume of blood collected in the bedpan to ascertain the total blood loss in the first hour after delivery"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"There were no withdrawals after randomisation and all outcomes were analysed in the allocated group." However the primary outcome data of 1 study participant in the placebo group were unavailable
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised

Funding source	Low risk	The study was supported by funding from the South African Medical Research Council (public funding) and University of the Witwatersrand (the institution of the authors)

Hofmeyr 2011

Methods	2-arm placebo-controlled randomised trial.
Participants	Between 6th March 2006 and 13th August 2007, 1103 parturients were randomised in a hospital setting in South Africa, Uganda, and Nigeria. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing caesarean section or instrumental delivery, or those who declined participation or were unable to consent, were too ill or distressed to participate or with a not viable pregnancy
Interventions	400 mcg plus 10 IU of misoprostol plus oxytocin administered sublingually plus intramuscularly (n = 547) versus 10 IU of oxytocin administered intramuscularly (n = 556)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, manual removal of placenta, death, blood loss (mL), fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers were stratified by country in blocks of 6-8
Allocation concealment (selection bias)	Low risk	The trial medication was provided, and the study drug packs were prepared, by Gynuity Health Projects. 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. Enrolment 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

Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was "double-blind." "The packs were identical in shape, colour, weight, and feel, and contained either 2 tablets of 200 mcg of misoprostol (HRA Pharma, Paris, France) or 2 matching placebo tablets."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Low risk	Similarly to the study team of Gulmezoglu 2001, investigators evaluated blood loss by collection with a fresh non-absorbent sheet and low plastic "fracture" bedpan placed under the mother from as soon as possible after delivery until 1 hour postpartum. Investigators considered that "longer-term blood loss measurement is more difficult to standardise." They transferred the blood collected in the sheet and the bedpan (together with any soaked small gauze swabs) to a measuring jar to ascertain the volume. Alternatively, they collected blood with a plastic sheet placed under the mother immediately after delivery. If bleeding continued beyond 1 hour, investigators restarted collection and measurement until bleeding subsided. Attempts were made to minimise any losses on the drapes and gowns of delivery attendants. In addition, "the placental interstices also contain maternal blood (about 9% of 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
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Data for the primary outcome were not available for 4 of the 1103 women."
Selective reporting (reporting bias)	High risk	The prospectively registered protocol of the study (ClinicalTrials.gov NCT 00124540) lists some secondary outcomes different to those included the study report (at least 1000 mL within the first hour only, transfusion, Hb less than 8 g/dL 24 hours after delivery)

Hofmeyr 2011   *(Continued)*

Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by funding from Gynuity Health Projects through a grant from the Bill and Melinda Gates Foundation (public funding)

Hoj 2005

Methods	2-arm placebo-controlled randomised trial.
Participants	Between March 2003 and August 2004, 661 parturients were randomised in a community setting in Guinea-Bissau. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria were not specified
Interventions	600 mcg of misoprostol administered sublingually (n = 330) versus placebo or control (n = 331)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, manual removal of placenta, death, blood loss (mL), change in Hb level, third-stage duration (min), nausea, vomiting, fever, shivering
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using a list of random numbers.
Allocation concealment (selection bias)	Low risk	Investigators used opaque envelopes that were consecutively-numbered and filled with the study drugs
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Misoprostol and placebo tablets of identical form, size, colour, and packing were produced."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.

Objective assessment of blood loss	Low risk	After delivery of the baby and drainage of the amniotic fluid, investigators placed a clean plastic-lined absorbent drape under the mother. They changed the drape as many times as needed. The mother stayed on the drape or was asked to wear a pad over the next 60 minutes. All drapes and pads were weighed with an electronic scale and the known dry weights were subtracted in order to ascertain the volume of blood loss on the basis that 1 g is equivalent to 1 mL
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by funding from the Danish Society of Obstetrics and Gynaecology, the Illum Foundation, and the Danish International Development Agency (public funding)

Hong 2007

Methods	2-arm placebo-controlled randomised trial.
Participants	Between dates unspecified, 214 parturients were randomised in a hospital setting in Korea. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at high risk for PPH, who delivered by caesarean (unspecified whether elective or emergency). Exclusion criteria were not specified
Interventions	20 IU of oxytocin administered by an intravenous infusion (n = 118) versus 400 mcg plus 20 IU of misoprostol plus oxytocin administered rectally plus by an intravenous infusion (n = 96)
Outcomes	The study recorded the following outcomes: additional uterotonics, transfusion, change in Hb level, fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and caregivers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessor blinding was not reported, but the use of placebo impeded knowledge of treatment allocations
Objective assessment of blood loss	Unclear risk	Methods of evaluating blood loss were not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Is 2012

Methods	2-arm active-controlled randomised trial.
Participants	Between dates unspecified, 200 parturients were randomised in a hospital setting in India. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria were not specified
Interventions	400 mcg of misoprostol administered rectally (n = 100) versus unspecified of ergometrine administered intramuscularly (n = 100)

Outcomes	The study recorded the following outcomes: third-stage duration (min), nausea, vomiting, shivering
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and caregivers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Unclear risk	Methods of evaluating blood loss were not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Jago 2007

Methods	2-arm active-controlled randomised trial.
Participants	Between January 2001 and December 2002, 510 parturients were randomised in a hospital setting in Nigeria. The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing induction or augmentation of labour or instrumental delivery, or those requiring epidural analgesia or with hypertension in pregnancy, existing hypertension, chronic renal disease, diabetes, vascular diseases, cardiac disease, anticoagulation therapy or allergy to ergometrine or oxytocin
Interventions	500 mcg of ergometrine administered intramuscularly (n = 254) versus 10 IU of oxytocin administered by an intravenous bolus (n = 256)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, blood loss (mL), hypertension
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using a computer-generated list of random numbers
Allocation concealment (selection bias)	Unclear risk	Investigators used numbers that were labelled on envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and caregivers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Unclear risk	Methods of evaluating blood loss were not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were

		randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Jangsten 2011

Methods	2-arm controlled randomised trial.
Participants	Between November 2006 and April 2008, 1802 parturients were randomised in a hospital setting in Sweden. The population comprised women of parity 4 or less, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing elective caesarean section, or those who were non-Swedish speaking or with previous PPH, pre-eclampsia, grand multiparity (more than 4) or intrauterine death
Interventions	10 IU of oxytocin administered by an intravenous bolus (n = 903) versus of placebo or control (n = 899)
Outcomes	The study recorded the following outcomes: PPH at 1000, transfusion, manual removal of placenta, blood loss (mL), change in Hb level, third-stage duration (min)
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation was computer-generated.
Allocation concealment (selection bias)	Low risk	Investigators used sealed envelopes containing the randomisation group prepared in consecutive order and kept in another unit. At randomisation, midwives phoned the staff at the other unit who opened the envelopes and disclosed the assigned intervention and trial number
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Because of the nature of the study, blinding was not possible for the midwives, but the parturients were not informed of which management was to be used for them."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessors were not blinded to treatment allocations.

Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by removing pads soaked with amniotic fluid and placing a dry sanitary pad under the mother, immediately after the birth of the baby. They weighed all sanitary towels and pads before and after use. Blood loss was recorded (a) between the birth of the baby and the expulsion of the placenta, and (b) from expulsion of the placenta up to 2 hours postpartum
Incomplete outcome data (attrition bias) All outcomes	Low risk	171 randomised women were not included in the study analysis. Among those randomised to receive oxytocin, 4 withdrew consent, 75 had caesareans, and 14 were lost to follow-up. In the control group, 2 withdrew consent, 56 had caesareans, and 20 were lost to follow-up
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	High risk	The authors excluded 131 randomised study participants from the analysis because they experienced caesarean deliveries
Funding source	Low risk	The study was supported by funding from the Research and Development Board in Göteborg and Bohuslän, Baby Bag and the SU Foundation in Sweden (public funding)

Jerbi 2007

Methods	2-arm controlled randomised trial.
Participants	Between February 2005 and March 2005, 130 parturients were randomised in a hospital setting in Tunisia. The population comprised women of parity 5 or less, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients with placenta praevia, antepartum haemorrhage, non-cephalic presentation, intrauterine death, grand multiparity, (more than 5), fibroids, anticoagulation therapy, previous PPH or previous caesarean
Interventions	5 IU of oxytocin administered by an intravenous bolus (n = 65) versus placebo or control (n = 65)
Outcomes	The study recorded the following outcomes: PPH at 1000, transfusion, manual removal of placenta, death, change in Hb level, third-stage duration (min)
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Jerbi 2007 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and caregivers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Unclear risk	Methods of evaluating blood loss were not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were unclear.

Jirakulsawas 2000

Methods	2-arm active-controlled randomised trial.
Participants	Between 1st June 1998 and 31st December 1998, 140 parturients were randomised in a hospital setting in Thailand. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at unspecified for PPH, who delivered by vaginal delivery. Exclusion criteria were not specified
Interventions	600 mcg of misoprostol administered orally (n = 70) versus 200 mcg of ergometrine administered intramuscularly (n = 70)
Outcomes	The study recorded the following outcomes: PPH at 500, blood loss (mL)

Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and care-givers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Unclear risk	Methods of evaluating blood loss were not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Karkanis 2002

Methods	2-arm active-controlled randomised trial.
Participants	Between dates unspecified, 238 parturients were randomised in a hospital setting in Canada. The population comprised women of parity 5 or less, unspecified whether singleton or multiple pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients with coagulopathy, anticoagulation therapy, previous PPH or previous caesarean

Interventions	400 mcg of misoprostol administered rectally (n = 100) versus 5 IU of oxytocin administered by an intravenous bolus or intramuscularly (n = 113). There were 15 exclusions post randomisation but it was unclear from which group
Outcomes	The study recorded the following outcomes: additional uterotonics, transfusion, manual removal of placenta, change in Hb level. third-stage duration (min), nausea, vomiting, headache, fever, shivering, abdominal pain
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A statistician developed blocked randomisation tables for each centre
Allocation concealment (selection bias)	Low risk	Pharmacy assembled consecutively-numbered opaque, sealed packets that contained the group allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study participants and caregivers were not blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessors were not blinded to treatment allocations.
Objective assessment of blood loss	Unclear risk	Methods of evaluating blood loss were not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"13 women randomised subsequently delivered by caesarean and were excluded from analysis. 2 women were lost to follow-up early in the trial when their packets were opened but the manoeuvre was not completed and no data were recorded."
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	High risk	Not all study participants were included in the analysis.
Funding source	Low risk	The study was supported by funding from the physicians of Ontario, through the

	Physician Services Incorporated Foundation (public funding)

Kerekes 1979

Methods	3-arm controlled randomised trial.
Participants	Between dates unspecified, 140 parturients were randomised in a hospital setting in Hungary. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at unspecified for PPH, who delivered by vaginal delivery. Exclusion criteria were not specified
Interventions	200 mcg of ergometrine administered by an intravenous bolus (n = 50) versus placebo or control (n = 43) versus 1 mg dinoprost administered intramuscularly (n = 47). The dinoprost arm was not included in the analysis
Outcomes	The study recorded the following outcome: third-stage duration (min)
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and caregivers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Unclear risk	Investigators evaluated blood loss by collection in a container placed under the mother during the third stage of labour until 2 hours postpartum. The contents of the container were transferred to a measuring cylinder. However, blood loss data were not reported in a format that could be extracted for the purpose of this review
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants

Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Khan 1995

Methods	2-arm active-controlled double-blinded randomised trial.
Participants	Between 1st January 1991 and 30th June 1991, 2040 parturients were randomised in a hospital setting in United Arab Emirates. The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing induction or augmentation of labour, caesarean section or instrumental delivery, or requiring general anaesthesia, epidural or diazepam, or those with antenatal hypertension (160/100 mmHg or more), hypertension on antihypertensive drugs, multiple pregnancy, cardiac disease or Hb of 90 g/L or less
Interventions	10 IU of oxytocin administered intramuscularly (n = 1017) versus 500 mcg plus 5 IU of ergometrine plus oxytocin administered intramuscularly (n = 1023)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, transfusion, manual removal of placenta, vomiting, headache
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Treatment was allocated as per a number code generated by the hospital pharmacist who alone was aware of the content of the ampoules
Allocation concealment (selection bias)	Low risk	Participants were assigned an opaque sealed envelope. Each envelope carried the instruction to use a numbered vial of the study drug

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study participants and caregivers were blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss "in the standard way" by measurement of blood and clots in a graduated jug, and by weighing swabs and linen
Incomplete outcome data (attrition bias) All outcomes	Low risk	"12 patients had to be excluded from the trial (oxytocin 5; syntometrine [ergometrine plus oxytocin] 7) after randomisation because they no longer fulfilled the inclusion criteria... [including] 2 who required caesarean section (1 in each group) and 10 who were delivered by forceps or ventouse (oxytocin 4; syntometrine [ergometrine plus oxytocin] 6)."
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	High risk	Those who withdrew from the study after randomisation were not included in the analysis
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Kikutani 2006

Methods	4-arm active-controlled randomised trial.
Participants	Between dates unspecified, 136 parturients were randomised in a hospital setting in Japan. The population comprised women of unspecified parity, either singleton or multiple pregnancy, at high risk for PPH, who were scheduled for caesarean with ASA I or II. Exclusion criteria comprised parturients that were affected by cardiovascular conditions, were scheduled for autologous blood transfusion, who had tocolytics administered or premature rupture of membranes
Interventions	10 IU up to 20 IU of oxytocin administered by an intravenous bolus (n = 102) versus 200 mcg ergometrine administered by an intravenous bolus (n = 34)

Outcomes	The study recorded the following outcome: blood loss (mL).
Notes	Contact with study authors for additional information: no. Additional data from authors: no and data cannot be extracted for meta-analysis. Manuscript translated from Japanese in full

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Methods of blinding were not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Objective assessment of blood loss	Unclear risk	Methods of evaluating blood loss were not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	Not reported.
Funding source	Unclear risk	Not reported.

Kumru 2005

Methods	2-arm active-controlled randomised trial.
Participants	Between August 2003 and March 2004, 55 parturients were randomised in a hospital setting in Turkey. The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by either elective or emergency caesarean. Exclusion criteria comprised parturients with multiple pregnancy, hypertension or vascular diseases

Kumru 2005 *(Continued)*

Interventions	10 IU of oxytocin administered by an intravenous bolus plus infusion (n = 35) versus 200 mcg plus 10 IU of ergometrine plus oxytocin administered by an intravenous bolus plus by intravenous bolus plus infusion (n = 20)
Outcomes	The study recorded the following outcome: blood loss (mL).
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and care-givers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Low risk	Investigators evaluated intraoperative blood loss by weighing compresses and rolls before and after the birth of the baby, and calculating the difference between these measurements. Pre-weighted pads were distributed in advance to each mother, and collected at intervals of 3-6 hours hour intervals after the aspiration of amniotic fluid
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised

Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Kundodyiwa 2001

Methods	2-arm placebo-controlled randomised trial.
Participants	Between October 1999 and February 2000, 500 parturients were randomised in a hospital setting in Zimbabwe. The population comprised women of unspecified parity, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing instrumental delivery, or those with previous PPH, antepartum haemorrhage, coagulopathy, multiple pregnancy, asthma or allergies to prostaglandins or oxytocin
Interventions	400 mcg of misoprostol administered orally (n = 243) versus 10 IU of oxytocin administered intramuscularly (n = 256). There was 1 exclusion post randomisation but it was unclear as to which group it was randomised to
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, additional uterotonics, transfusion, manual removal of placenta, death, blood loss (mL) , third-stage duration (min), nausea, vomiting, fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using a computer-generated random sequence
Allocation concealment (selection bias)	Low risk	The participant was asked to randomly pick a numbered sealed opaque envelope from the study cooler-box
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Identical placebo tablets could not be obtained from the manufacturers. The tablets were similar in size and colour but not in shape. However, most reviewed trials on misoprostol had this similar problem although this method of blinding proved to be effective."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"The data sheet was completed by the midwife supervising the delivery and collected and checked by the research assistant."

Objective assessment of blood loss	Low risk	After delivery, investigators evaluated blood loss by removing linen soiled with amniotic fluid, and then placing a fresh disposable incontinence pad with a plastic backing under the mother. Blood expressed from the uterus was measured with a calibrated measuring jug. The volume of blood soiling linen savers and sanitary pads was determined as the difference between dry weights and soiled weights: these measurements were added to the volume recorded by the calibrated jug
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Data for 1 woman were excluded because she delivered undiagnosed twins after randomisation."
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Lam 2004

Methods	2-arm active-controlled randomised trial.
Participants	Between dates unspecified, 60 parturients were randomised in a hospital setting in China (Hong Kong SAR). The population comprised women of unspecified parity, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing induction or augmentation of labour, or those with antepartum haemorrhage, anaemia, 2 or more surgical terminations, previous manual removal of placenta, previous PPH or previous third stage complications
Interventions	500 mcg plus 5 IU of ergometrine plus oxytocin administered by an intravenous bolus (n = 30) versus 600 mcg of misoprostol administered sublingually (n = 30)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, additional uterotonics, manual removal of placenta, death, fever
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Treatment was allocated using a random number-generated table
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study participants and caregivers were not blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss during the third stage by visual estimation, and by objective measurement on the basis of a method previously described by Newton et al. Whilst any blood clots were collected and measured with a jug, white linen was placed under the mother during delivery and subsequently processed for 15 minutes with sodium hydroxide solution in an automatic stomacher (laboratory blender), to achieve the formation of alkaline hematin. "The optical density at 550 nm of the alkaline hematin was measured by spectrophotometry and compared with that of a known volume of a sample of the patient's venous blood" to calculate the volume of blood loss
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	It was unclear from the study report whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Lapaire 2006 *(Continued)*

Methods	2-arm active-controlled double-blinded randomised trial.	
Participants	Between January 1999 and February 2002, 56 parturients were randomised in a hospital setting in Switzerland. The population comprised women of unspecified parity, either singleton or multiple pregnancy, at high risk for PPH, who delivered by elective caesarean section. Exclusion criteria comprised parturients undergoing emergency caesarean section, or those with fetal distress, fetal malformations, pre-eclampsia, HELLP syndrome, coagulopathy, severe systemic disorders, an American Society of Anaesthesiologists physical status of 3 or greater, severe asthma, previous myomectomy, pyrexia (more than 38. 5°C) or hypersensitivity to prostaglandins	
Interventions	25 IU of oxytocin administered by an intravenous bolus plus infusion (n = 28) versus 800 mcg plus 5 IU of misoprostol plus oxytocin administered orally plus by an intravenous bolus (n = 28)	
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, death, blood loss (mL), nausea, headache, shivering	
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The hospital pharmacy performed the 1: 1 computer-generated randomisation that assigned the participants to their group
Allocation concealment (selection bias)	Low risk	Investigators used identical study boxes from pharmacy.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was "double-blind": "the study drugs and placebos [were provided by the pharmacy] in unidentifiable form."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Low risk	When the membranes ruptured before delivery, investigators evaluated intraoperative and postoperative blood loss by determining the difference in weight of cloths and pads used to absorb blood during surgery and in the intermediate care unit. When membranes did not rupture preoperatively, investigators evaluated blood loss by collection in suction bottles and sub-

Lapaire 2006   (*Continued*)

		tracting estimated amniotic fluid volume. Investigators considered that 1 g is equivalent to 1 mL of blood or amniotic fluid
Incomplete outcome data (attrition bias) All outcomes	Low risk	"3 patients in the oxytocin group were excluded from statistical analysis because of errors in drug administration." Moreover calculated blood loss data were unavailable in 13 cases and for these women the primary outcome was estimated clinically
Selective reporting (reporting bias)	High risk	The study protocol that was registered retrospectively (ClinicalTrials.gov) lists PPH as the primary outcome of the study, but the study report lists the primary outcomes as intraoperative and postoperative blood loss and drug-related adverse effects (these items are listed only as secondary outcomes in the registration file). The study does not report the incidence of PPH at 500 mL, nor PPH at 1000 mL
Intention to treat analysis	High risk	The authors excluded 3 study participants in the oxytocin group from the analysis because they incurred errors in drug administration
Funding source	Low risk	The study was supported by funding from the Scientific Pool of Basel University Hospital (the institution of the authors)

Leung 2006

Methods	2-arm active-controlled double-dummy randomised trial.
Participants	Between July 2004 and March 2005, 329 parturients were randomised in a hospital setting in Hong Kong. The population comprised women of parity 4 or less, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients requiring prophylactic oxytocin infusion, or those with pre-existing hypertension, pre-eclampsia, asthma, cardiac/renal/liver diseases, grand multiparity or fibroids
Interventions	100 mcg of carbetocin administered intramuscularly (n = 165) versus 500 mcg plus 5 IU of ergometrine plus oxytocin administered intramuscularly (n = 164)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, manual removal of placenta, blood loss (mL), change in Hb level, third-stage duration (min), nausea, vomiting, hypertension, headache, tachycardia, shivering

Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using a computer-generated code before recruitment
Allocation concealment (selection bias)	Low risk	This was performed by opening a sealed, consecutively-numbered, opaque envelope
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study participants and caregivers were blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss by visual estimation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"15 women in the carbetocin group and 14 women in the syntometrine [ergometrine plus oxytocin] group failed to have a paired haemoglobin test to measure the change in haemoglobin 48 hours after delivery either because they had requested early home discharge or refused."
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification, but not all of the outcomes projected by methodological descriptions were reported as results in the study report (cases of fever were omitted)
Intention to treat analysis	High risk	Those who withdrew from the study after randomisation were not included in the analysis
Funding source	High risk	The study was supported by funding from Ferring Pharmaceuticals

Lokugamage 2001

Methods	2-arm active-controlled randomised trial.
Participants	Between dates unspecified, 40 parturients were randomised in a hospital setting in the UK. The population comprised women of unspecified parity, either singleton or multiple pregnancy, at high risk for PPH, who delivered by either elective or emergency caesarean. Exclusion criteria comprised parturients with 2 or more previous caesarean sections or previous uterine rupture
Interventions	10 IU of oxytocin administered by an intravenous bolus (n = 20) versus 500 mcg of misoprostol administered orally (n = 20)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, blood loss (mL), change in Hb level, fever, shivering
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was undertaken by means of computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Investigators used sealed opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"The obstetrician, surgical assistant, scrub nurse and recovery midwife were blinded to the treatment. The anaesthetist and the anaesthetic assistant were not blinded as it was important for patient safety that a record was kept of all drugs administered."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	High risk	Investigators evaluated intraoperative and postoperative (up to 1 hour) blood loss by visual estimation "in a standard manner (volume of blood in suction bottle plus soiling of swabs and bed sheets)."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.

Lokugamage 2001 *(Continued)*

Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by "assistance" from the Department of Anaesthesia at University College London Hospitals NHS Trust (the institution of the authors)

Lumbiganon 1999

Methods	3-arm active-controlled double-dummy randomised trial.
Participants	Between dates unspecified, 597 parturients were randomised in a hospital setting in South Africa and Thailand. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing elective caesarean section or abortion, or those with asthma, other severe chronic allergic conditions a contraindication to use of misoprostol or if they were not willing or able to give informed consent
Interventions	600 mcg or 400 mcg of misoprostol administered orally (n = 397) versus 10 IU of oxytocin administered intramuscularly (n = 200)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, manual removal of placenta, death, blood loss (mL), nausea,. vomiting, fever, shivering
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A random allocation sequence was generated centrally.
Allocation concealment (selection bias)	Low risk	The treatment packs were consecutively-numbered and sealed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The packs were identical in shape, colour, weight and feel. Each woman received an injection and 3 tablets. Thus, the trial was double-blinded using double placebos."

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss from the delivery of the baby until the mother was transferred to postnatal care. The collected blood was poured into a standard measuring jar provided by WHO for the purpose of volumetric measurement. Linen was not weighed but clots and small gauze swabs soaked with blood were included in the measurement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusion after randomisation: "8 women did not comply with treatment in the oxytocin group (6 because of emergency caesarean section, 1 was HIV positive (mistakenly excluded despite HIV sero-positivity not being an exclusion criterion), and in another case the ampoule could not be located in the treatment pack. There was 1 woman in the misoprostol 600 mcg group who did not comply with the treatment, because the tablets could not be located after the treatment pack was opened. Finally, in the misoprostol 400 mcg group, 1 woman had an emergency caesarean section after the treatment pack was opened and could not receive the allocated treatment."
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by funding from the WHO (public funding). Active and placebo medications, syringes and swabs were donated by Searle, Novartis Pharma AG and Becton Dickinson International

Maged 2016

Methods	2-arm active-controlled double-dummy randomised trial.
Participants	Between May 2013 and December 2014, 200 parturients were randomised in a hospital setting in Egypt. The population comprised women of unspecified parity, either singleton or multiple pregnancy, at high risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients with placenta praevia, coagulopathy, pre-eclampsia, cardiac/renal/liver disorders, epilepsy or known hypersensitivity to oxytocin or carbetocin
Interventions	100 mcg of carbetocin administered intramuscularly (n = 100) versus 5 IU of oxytocin administered intramuscularly (n = 100)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, blood loss (mL), change in Hb level, third-stage duration (min) , nausea, vomiting, headache, tachycardia, shivering
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were equally randomised using an automated web-based randomisation system
Allocation concealment (selection bias)	Unclear risk	The study report states that investigators ensured allocation concealment, but gives no further details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study participants and caregivers were blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss by weighing swabs and using pictorial charts
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.

Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

McDonald 1993

Methods	2-arm active-controlled double-blinded randomised trial.
Participants	Between 19th February 1990 and 20th October 1991, 3497 parturients were randomised in a hospital setting in Australia. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing emergency or elective caesarean section, or requiring general anaesthetic for instrumental delivery, or those with hypertension in labour (more than 150/100 mmHg), antenatal hypertension, maternal distress, advanced stage in labour, language barrier, fetal abnormality, intrauterine death or medical disorder
Interventions	500 mcg plus 5 IU of ergometrine plus oxytocin administered intramuscularly (n = 1730) versus 10 IU of oxytocin administered intramuscularly (n = 1753). There were 14 exclusions post randomisation but it was unclear from which group
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, manual removal of placenta, NNU admissions, breastfeeding, nausea, vomiting
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The ampoules were numbered by Sandoz using simple randomisation. There was no blocking or prognostic stratification
Allocation concealment (selection bias)	Low risk	The ampoules were numbered by third party (Sandoz).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Delivery attendants were blinded to treatment allocations.

McDonald 1993 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss by the estimation of attending obstetricians and midwives
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All women allocated to receive a drug were included in that group, excluding only the 14 women for whom drug allocation was not recorded."
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	High risk	The study was supported by funding from Sandoz.

Mitchell 1993

Methods	2-arm active-controlled double-blinded randomised trial.
Participants	Between dates unspecified in 1984, 461 parturients were randomised in a hospital setting in UK. The population comprised women of unspecified parity, either singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing elective caesarean section, or those with significant hypertension or cardiac disease
Interventions	500 mcg plus 5 IU of ergometrine plus oxytocin administered intramuscularly (n = 230) versus 5 IU of oxytocin administered intramuscularly (n = 231)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, manual removal of placenta, blood loss (mL), third-stage duration (min)
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement

Mitchell 1993 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Unclear sequence: described as without any blocking or stratification
Allocation concealment (selection bias)	Low risk	Investigators used identical study boxes prepared by third party (Sandoz)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study participants and caregivers were blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss "in the standard way by graduated jug measurement plus an allowance for spillage."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by funding from the Perinatal Trials Service (public funding), for the Department of Health for England and Wales, and for Birthright (the charitable arm of the RCOG). Coded medication ampoules were provided by Sandoz

Mobeen 2011

Methods	2-arm placebo-controlled randomised trial.
Participants	Between June 2006 and June 2008, 1119 parturients were randomised in a community setting in Pakistan. The population comprised women of unspecified parity, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients with hypertension, non-cephalic presentation, polyhydramnios, previous caesarean, multiple pregnancy, intrauterine death, antepartum haemorrhage or Hb less than 80 g/L

Interventions	600 mcg of misoprostol administered orally (n = 534) versus placebo or control (n = 585)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, manual removal of placenta, death, blood loss (mL), change in Hb level, third-stage duration (min), nausea, vomiting, headache, fever. shivering
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated random code in blocks of 6 was maintained by Gynuity Health Projects in New York and not revealed until data collection and cleaning were completed
Allocation concealment (selection bias)	Low risk	Study medication was packed in numbered colour-coded boxes by Gynuity Health Projects in New York
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Both women and TBAs were blinded to study assignment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Low risk	To evaluate postpartum blood loss, blood was collected with a perineal sheet and bedpan placed under the mother for a minimum of 1 hour or until active bleeding stopped (whichever occurred last). "Blood collected in the bedpan was transferred to a measuring jar, which was then closed, and the perineal sheet and cotton roll were placed in a sealed plastic bag. The closed measuring jar and sealed plastic bag were then placed inside a plastic cooler which was tightly closed and stored in a secure place in the woman's home until the local health visitor or community health nurse arrived for weighing, 1-2 days after delivery."

Incomplete outcome data (attrition bias) All outcomes	Low risk	"Invalid blood loss measures, which mainly occurred when monitoring visits were not possible because of poor weather conditions, were excluded from our analysis."
Selective reporting (reporting bias)	Low risk	The study report matches the study protocol that was registered (ClinicalTrials.gov NCT00120237)
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by funding from the Bill and Melinda Gates Foundation (public funding)

Moertl 2011

Methods	2-arm active-controlled double-blinded randomised trial.
Participants	Between January 2008 and July 2008, 84 parturients were randomised in a hospital setting in Austria. The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by elective caesarean section. Exclusion criteria comprised parturients requiring general anaesthesia, or those with placenta praevia, placental abruption, multiple pregnancy, pre-eclampsia, gestational diabetes, pre-existing insulin-dependent diabetes, cardiovascular/renal disorders, hypo-/hyperthyroidism or women on cardiovascular system medications
Interventions	100 mcg of carbetocin administered by an intravenous bolus (n = 28) versus 5 IU of oxytocin administered by an intravenous bolus (n = 28). There were 28 exclusions post randomisation but it was unclear from which group
Outcomes	The study recorded the following outcomes: additional uterotonics. change in Hb level, nausea, headache
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by a computer-generated randomisation sequence in a 1:1 ratio with blocks of 10 and no stratification

Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Study medication was double-blinded to the clinical staff (obstetricians as well as anaesthesiologists) and the technicians performing the measurements."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Unclear risk	Investigators did not evaluate blood loss.
Incomplete outcome data (attrition bias) All outcomes	High risk	After randomisation, investigators excluded 28 women from analysis for technical problems (n = 15), change to general anaesthesia (n = 9), recording artefacts (n = 3) and patient withdrawal (n = 1)
Selective reporting (reporting bias)	Low risk	The study report matches the study protocol that was registered (EudraCT 2007-005498-78)
Intention to treat analysis	High risk	Not all study participants were included in the analysis.
Funding source	Low risk	CNSystems Medizintechnik AG in Graz, Austria provided the Task Force® Monitor 3040i system used to measure haemodynamic parameters. No other external funding was required for the study

Moir 1979

Methods	2-arm active-controlled randomised trial.
Participants	Between dates unspecified, 88 parturients were randomised in a hospital setting in the UK. The population comprised women of primigravidas, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria were not specified
Interventions	500 mcg of ergometrine administered by an intravenous bolus (n = 44) versus 10 IU of oxytocin administered by an intravenous bolus (n = 44)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, blood loss (mL) , nausea
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and care-givers) was unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by "the haemoglobin extraction-dilution technique, which is acceptably accurate (Roe, Gardiner and Dudley, 1962; Thornton et al, 1963) and particularly suited to obstetric use (Moir and Wallace, 1967; Wallace, 1967). The pedometer apparatus was used and all blood and blood-stained linen were collected."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Moodie 1976

Methods	2-arm active-controlled randomised trial.
Participants	Between dates unspecified, 148 parturients were randomised in a hospital setting in the UK. The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by vaginal delivery. Exclusion criteria were not specified

Interventions	500 mcg of ergometrine administered by an intravenous bolus (n = 78) versus 5 IU of oxytocin administered by an intravenous bolus (n = 70)
Outcomes	The study recorded the following outcomes: PPH at 500, blood loss (mL), nausea
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and caregivers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by collection with the placenta bowl and soiled linen and swabs. "The principles of the haemoglobin extraction-dilution technique employed have been discussed by Roe, Gardiner and Dudley (1962) and Thornton and colleagues (1963)."
Incomplete outcome data (attrition bias) All outcomes	High risk	There were 148 study participants but blood loss data were available in only 80 cases
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Mukta 2013

Methods	2-arm active-controlled randomised trial.
Participants	Between May 2010 and October 2011, 200 parturients were randomised in a hospital setting in India. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing emergency or elective caesarean section, or those with eclampsia, asthma, epilepsy, cardiac/kidney disorder or coagulopathy
Interventions	600 mcg of misoprostol administered orally (n = 100) versus 10 IU of oxytocin administered intramuscularly (n = 100)
Outcomes	The study recorded the following outcomes: PPH at 500, additional uterotonics, nausea, vomiting, fever, shivering, abdominal pain
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomly divided into 2 equal groups.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and caregivers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Unclear risk	Investigators evaluated blood loss in mL, by collection with a calibrated plastic drape, after the drainage of amniotic fluid and delivery of the baby until the third stage of labour was completed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the

		analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Musa 2015

Methods	2-arm active-controlled double-dummy randomised trial.
Participants	Between 1st January 2013 and 30th June 2013, 235 parturients were randomised in a hospital setting in Nigeria. The population comprised women of parity 4 or less, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing planned instrumental, or those who received oxytocin and/or misoprostol other than in the third stage of labour, or those with grand multiparity (more than 4), multiple pregnancy, fibroids, polyhydramnios, pre-eclampsia, eclampsia, hypertension, cardiac disorder, asthma, antepartum haemorrhage previous PPH, prolonged rupture of membranes or Hb less than 100 g/L)
Interventions	600 mcg of misoprostol administered orally (n = 121) versus 10 IU of oxytocin administered intramuscularly (n = 114)
Outcomes	The study recorded the following outcomes: PPH at 500, morbidity, additional uterotonics, manual removal of placenta, death, blood loss (mL), change in Hb level, third-stage duration (min), nausea, vomiting, fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation was blocked (restrictive), using computer-generated random numbers prepared by an independent statistician
Allocation concealment (selection bias)	Unclear risk	Investigators used opaque envelopes but no other details provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Participants, caregivers, and outcome assessors (researchers or research assistants) were masked to group allocation. Investigators were not masked for data analysis."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Participants, caregivers, and outcome assessors (researchers or research assistants) were masked to group allocation. Investi-

		gators were not masked for data analysis."
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by "the gravimetric method" (Ambardekar 2009) until 1 hour after delivery
Incomplete outcome data (attrition bias) All outcomes	High risk	235 study participants were randomised but only 200 were analysed due to protocol deviations and missing data
Selective reporting (reporting bias)	Unclear risk	The study protocol was registered retrospectively (PACTR 201407000825227)
Intention to treat analysis	High risk	Not all study participants were included in the analysis.
Funding source	Low risk	The study was supported by funding from the University of Ilorin Teaching Hospital (the institution of the authors)

Nasr 2009

Methods	2-arm active-controlled double-dummy randomised trial.
Participants	Between dates unspecified, 514 parturients were randomised in a hospital setting in Egypt. The population comprised women of unspecified parity, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing caesarean section, or those with antepartum haemorrhage, coagulopathy, hypertension in pregnancy or the need for anticoagulants
Interventions	800 mcg of misoprostol administered rectally (n = 257) versus 5 IU of oxytocin administered by an intravenous infusion (n = 257)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, additional uterotonics, transfusion, manual removal of placenta, death, third-stage duration (min), nausea, vomiting, fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment was allocated by a computer-generated random allocation system created at the Statistics Unit of Assiut University Hospital

Allocation concealment (selection bias)	Low risk	Allocation codes were placed in sealed, opaque, consecutively-numbered envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was "double-blind": active treatments and placebo treatments were "identical-looking."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss by the estimation of attending physicians
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were unclear.

Ng 2001

Methods	2-arm active-controlled randomised trial.
Participants	Between June 1998 and February 1999, 2058 parturients were randomised in a hospital setting in Hong Kong. The population comprised women of parity 3 or less, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients requiring oxytocin infusion in the third stage, or those with pre-eclampsia, cardiac disorder, asthma, grand multiparity (more than 3), fibroids or contraindications for the use of either misoprostol or syntometrine
Interventions	600 mcg of misoprostol administered orally (n = 1026) versus 500 mcg plus 5 IU of ergometrine plus oxytocin administered intramuscularly (n = 1032)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, additional uterotonics, transfusion, manual removal of placenta, death, blood loss (mL), change in Hb level, nausea, vomiting, hypertension, headache, fever, shivering

Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was based on a table of computer-generated blocks of random numbers
Allocation concealment (selection bias)	Low risk	Allocation was placed in consecutively-numbered opaque sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	"This was not a double-blinded study."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessors were not blinded to treatment allocations.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss by the estimation of attending physicians
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Ng 2007

Methods	2-arm active-controlled double-dummy randomised trial.
Participants	Between April 2000 and January 2001, 360 parturients were randomised in a hospital setting in Hong Kong. The population comprised women of parity 3 or less, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients requiring oxytocin infusion in the third stage, or those with pre-eclampsia, cardiac disorder, asthma, grand multiparity (more than 3), fibroids or contraindications for the use of either misoprostol or syntometrine

Interventions	400 mcg of misoprostol administered orally (n = 178) versus 500 mcg plus 5 IU of ergometrine plus oxytocin administered intramuscularly (n = 177). There were 5 exclusions post randomisation but it was unclear from which group
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, additional uterotonics, transfusion, manual removal of placenta, death, blood loss (mL), change in Hb level, nausea, vomiting, hypertension, headache, fever, shivering
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was based on a table of computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Investigators used consecutively-numbered and sealed opaque packages
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The placebo was identical in size and colour but had a different shape to the misoprostol tablet. All women were asked to swallow the tablets directly from the opaque cup without looking at them. The identity of the active medication and placebo were concealed from the caregivers and the parturient."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss by the estimation of attending physicians
Incomplete outcome data (attrition bias) All outcomes	Low risk	"5 women were excluded from the analysis because of missing post-delivery haemoglobin level."
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification, but not all of the outcomes projected by methodological descriptions were reported as results in the study report (cases of tachycardia and dizziness were omitted)

Intention to treat analysis	High risk	Those who withdrew from the study after randomisation were not included in the analysis
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Nirmala 2009

Methods	2-arm active-controlled randomised trial.
Participants	Between dates unspecified, 120 parturients were randomised in a hospital setting in Malaysia. The population comprised women of unspecified parity, either singleton or multiple pregnancy, at high risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients younger than 18 years old, or those with cardiac disorder, hypertension requiring treatment, liver/renal/vascular/endocrine disorder (excluding gestational diabetes) or hypersensitivity to oxytocin or carbetocin
Interventions	100 mcg of carbetocin administered intramuscularly (n = 60) versus 500 mcg plus 5 IU of ergometrine plus oxytocin administered intramuscularly (n = 60)
Outcomes	The study recorded the following outcomes: PPH at 500, morbidity, additional uterotonics, transfusion, manual removal of placenta, death, blood loss (mL), change in Hb level, nausea, vomiting, hypertension, headache, shivering, abdominal pain
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation was computer-generated.
Allocation concealment (selection bias)	Unclear risk	Investigators used sealed, sequentially-numbered envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"The preparation and administration of the medication was carried out by midwives who were not involved in the management of the patient except for the drug administration."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.

Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by "the gravimetric method" from immediately after drug administration. They used a digital scale (Soehnle, Venezia) for weight measurement. In order to minimise confounding by fluid absorbed into drapes, they collected blood with a new plastic sheet placed under the mother after delivery of the baby. They also weighed any gauzes, tampons and pads used in the first hour after delivery of the placenta, and subtracted the dry weights of these materials to calculate blood loss on the basis that 1 g is equivalent to 1 mL
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Nordstrom 1997

Methods	2-arm placebo-controlled randomised trial.
Participants	Between 16th December 1993 and 6th October 1994, 1000 parturients were randomised in a hospital setting in Sweden. The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria were not specified
Interventions	10 IU of oxytocin administered by an intravenous bolus (n = 513) versus placebo or control (n = 487)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, manual removal of placenta, blood loss (mL), third-stage duration (min)
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation was computer-generated.
Allocation concealment (selection bias)	Low risk	Ampoules were prepared at the hospital pharmacy and consecutively-numbered
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The content of the ampullas was unknown to mothers, midwives and doctors until the study was completed."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss "by measuring collected blood and adding what was estimated to have been absorbed by surgical cloths and tissues."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by funding from the County Council and County Health Authority Research and Development Foundation in the County of Jämtland, Sweden (public funding)

Oboro 2003

Methods	2-arm active-controlled double-dummy randomised trial.
Participants	Between August 2000 and July 2001, 496 parturients were randomised in a hospital setting in Nigeria. The population comprised women of parity 4 or less, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing induction or augmentation of labour, or those with previous caesarean, Hb less than 80 g/L, previous PPH, grand multiparity (not defined), multiple pregnancy, polyhydramnios, fibroids or precipitate labour

Oboro 2003   (*Continued*)

Interventions	10 IU of oxytocin administered intramuscularly (n = 249) versus 600 mcg of misoprostol administered orally (n = 247)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, manual removal of placenta, death, blood loss (mL), change in Hb level, third-stage duration (min), nausea, vomiting, fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using random tables.
Allocation concealment (selection bias)	Low risk	Pharmacy prepared opaque sealed sequentially-numbered packets
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The identity of the active medication and placebo were concealed from the caregivers and parturients."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss by the estimation of attending obstetricians
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Ogunbode 1979

Methods	3-arm active-controlled randomised trial.
Participants	Between dates unspecified, 144 parturients were randomised in a hospital setting in Nigeria. The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing instrumental delivery, or those with previous PPH, multiple pregnancy, polyhydramnios or vaginal lacerations
Interventions	200 mcg or 500 mcg of ergometrine administered intramuscularly (n = 96) versus 500 mcg plus 5 IU of ergometrine plus oxytocin administered intramuscularly (n = 48)
Outcomes	The study recorded the following outcomes: PPH at 500, manual removal of placenta, blood loss (mL)
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Investigators performed restricted random allocation.
Allocation concealment (selection bias)	Unclear risk	Investigators used sealed sequentially-numbered envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"The identity of the various drugs was not known to the investigators until after completion of the trial."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss by collection in a dish pressed against the vulva for 3 minutes: the contents were carefully measured
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were

		randomised
Funding source	High risk	The study was supported by funding from Sandoz.

Orji 2008

Methods	2-arm active-controlled randomised trial.
Participants	Between January 2006 and September 2007, 600 parturients were randomised in a hospital setting in Nigeria. The population comprised women of parity 6 or less, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing caesarean section, or those with hypertension in pregnancy, packed cell volume less than 30%, previous PPH, haemoglobinopathy or cardiac disorder
Interventions	10 IU of oxytocin administered by an intravenous bolus (n = 297) versus 250 mcg of ergometrine administered by an intravenous bolus (n = 303)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, manual removal of placenta, blood loss (mL), change in Hb level, third-stage duration (min), nausea, vomiting, hypertension, headache
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation was done by sealed sequentially-numbered envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and care-givers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Unclear risk	Investigators evaluated blood loss by "using a pre-weighed gauze that was weighed again after delivery."

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification, but not all of the outcomes projected by methodological descriptions were reported as results in the study report (cases of transfusion and PPH at least 1000 mL were omitted)
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Ortiz-Gomez 2013

Methods	3-arm active-controlled randomised trial.
Participants	Between dates unspecified, 156 parturients were randomised in a hospital setting in Spain. The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by elective caesarean section. Exclusion criteria comprised parturients with comorbidities, refractory hypotension due to neuraxial blockage, vasoactive drugs needed to control haemodynamic issues or multiple pregnancy
Interventions	100 mcg of carbetocin administered by an intravenous bolus (n = 52) versus 61 IU of oxytocin administered by an intravenous bolus plus infusion (n = 104)
Outcomes	The study recorded the following outcomes: additional uterotonics, nausea, vomiting, headache, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using a computer-generated sequence
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.

Ortiz-Gomez 2013   *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and care-givers) was unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Unclear risk	Investigators evaluated blood loss by the estimation of delivery attendants, but blood loss data were not reported in a format way that could be extracted for the purpose of this review
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Owonikoko 2011

Methods	2-arm active-controlled randomised trial.
Participants	Between June 2006 and April 2007, 100 parturients were randomised in a hospital setting in Nigeria. The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by either elective or emergency caesarean. Exclusion criteria comprised parturients requiring general anaesthesia, or those with multiple pregnancy, placenta praevia, antepartum haemorrhage, cardiac/renal/liver disorders, coagulopathy, asthma, glaucoma, pre-eclampsia, eclampsia, prolonged labour or contraindications to administration of prostaglandins
Interventions	20 IU of oxytocin administered by an intravenous infusion (n = 50) versus 400 mcg of misoprostol administered sublingually (n = 50)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, blood loss (mL), change in Hb level, nausea, vomiting, headache, hypotension, shivering

Owonikoko 2011 *(Continued)*

Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The treatment allocation sequence was developed by a statistician who was not otherwise involved with the study using computer-generated table of random numbers and varied permutated blocks
Allocation concealment (selection bias)	Low risk	Investigators used sealed, opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"The anaesthetist was blind to the allocation until he opened each participant's envelope at surgery… The obstetricians were unaware of what oxytocic was given as the faces of the patients were screened off during the surgery."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"The obstetricians were unaware of what oxytocic was given as the faces of the patients were screened off during the surgery."
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by collection in a suction bottle, and by weighing delivery drapes and gauzes on the basis that 1 g is equivalent to 1 mL of blood. "Both the surgeon and anaesthetist estimated blood loss independently... The scrub nurse weighed the drapes and gauze before and after the operation, noted the amount of blood in the suction bottle, and recorded these... The postoperative care nurse also recorded the blood loss during the first 4 hours after surgery." Finally a research assistant (not part of the medical team) calculated the mean estimated blood loss from all these values
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.

Owonikoko 2011 (*Continued*)

Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Parsons 2006

Methods	2-arm active-controlled randomised trial.
Participants	Between April 2002 and October 2002, 450 parturients were randomised in a hospital setting in Ghana. The population comprised women of unspecified parity, either singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients with asthma, epilepsy or contraindications to prostaglandins
Interventions	10 IU of oxytocin administered intramuscularly (n = 225) versus 800 mcg of misoprostol administered orally (n = 225)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, additional uterotonics, transfusion, manual removal of placenta, death, blood loss (mL) , change in Hb level, third-stage duration (min), nausea, vomiting, hypertension, fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The treatment allocation was computer-generated.
Allocation concealment (selection bias)	Low risk	Investigators used sequentially-numbered, opaque, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	"We acknowledge that unblinding for some participants was possible because the envelopes for women who were initially randomised but who subsequently underwent caesarean section were returned and used for the next women enrolled."

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss by the estimation of attending physicians and midwives
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by funding from Matercare International and the Society of Obstetricians and Gynaecologists of Canada (public funding)

Parsons 2007

Methods	2-arm active-controlled randomised trial.
Participants	Between April 2002 and December 2002, 450 parturients were randomised in a hospital setting in Ghana. The population comprised women of unspecified parity, either singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients with asthma, epilepsy or contraindications to prostaglandins
Interventions	10 IU of oxytocin administered intramuscularly (n = 226) versus 800 mcg of misoprostol administered rectally (n = 224)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, additional uterotonics, transfusion, manual removal of placenta, death, blood loss (mL), change in Hb level, third-stage duration (min), nausea, vomiting, hypertension, fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Low risk	Investigators used sequentially-numbered, opaque, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Unblinding for some participants was possible because the envelopes for women who were initially randomised but who subsequently underwent caesarean section were returned and used for the next women enrolled."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss by the estimation of attending physicians and midwives
Incomplete outcome data (attrition bias) All outcomes	Low risk	Estimated blood loss data were unavailable in 9 cases (misoprostol 7; oxytocin 2) and Hb measurements (misoprostol 4; oxytocin 6) were unavailable in 10 cases
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by funding from Matercare International and the Society of Obstetricians and Gynaecologists of Canada (public funding)

Penaranda 2002

Methods	3-arm active-controlled randomised trial.
Participants	Between 29th October 2000 and 6th November 2000, 78 parturients were randomised in a hospital setting in Colombia. The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients with asthma, multiple pregnancy, intrauterine death, coagulopathy, cervical tear or water in the blood collector

Interventions	50 mcg of misoprostol administered sublingually (n = 25) versus 16 mLU/min of oxytocin administered by an intravenous infusion (n = 25) versus 200 mcg of ergometrine administered intramuscularly (n = 25). There were 3 exclusions post randomisation but it was unclear from which group
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, blood loss (mL), third-stage duration (min), vomiting, shivering
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and care-givers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Unclear risk	Investigators evaluated blood loss from cord clamping until 1 hour after delivery
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 women were excluded from the analysis after entering the study: "se excluyeron 3 pacientes por obito fetal, desgarro de cervix severo, vertimiento de agua en el recipiente recolector de sangre."
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	High risk	Not all study participants were included in the analysis.
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Prendiville 1988

Methods	2-arm controlled randomised trial.
Participants	Between 1st January 1986 and 31st January 1987, 1695 parturients were randomised in a hospital setting in the UK. The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients with cardiac disorder, antepartum haemorrhage, non-cephalic presentation, multiple pregnancy, intrauterine death but after change in the protocol multiple other exclusion criteria were introduced
Interventions	500 mcg plus 5 IU of ergometrine plus oxytocin administered intramuscularly (n = 846) versus of placebo or control (n = 849)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, manual removal of placenta, change in Hb level, NNU admissions, breastfeeding, vomiting, headache
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Low risk	Investigators used sequentially-numbered, opaque, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study participants and caregivers were not blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss by the estimation of attending physicians
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised

Funding source	Low risk	The study was supported by funding from the South Western Regional Health Authority of the United Kingdom (public funding)

Rajaei 2014

Methods	2-arm active-controlled double-dummy randomised trial.
Participants	Between dates unspecified, 400 parturients were randomised in a hospital setting in Iran. The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients with placenta praevia, placental abruption, coagulopathy, previous caesarean, macrosomia (more than 4 kg), polyhydramnios or uncontrolled asthma
Interventions	20 IU of oxytocin administered by an intravenous infusion (n = 200) versus 400 mcg of misoprostol administered orally (n = 200)
Outcomes	The study recorded the following outcomes: additional uterotonics, transfusion, blood loss (mL), change in Hb level, hypotension, fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment was allocated using simple randomisation with computer-generated numbers in a 1:1 ratio
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was "double-blind": "for blinding the study, identical-appearing solutions and tablets corresponding to the 2 pharmacological groups were prepared by the pharmacy and kept in the fridge until required."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Unclear risk	Investigators evaluated blood loss during the first hour after delivery, by collection with pads weighed before and after absorbance of blood

Rajaei 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data
Selective reporting (reporting bias)	Low risk	The study protocol was registered (ClinicalTrials.gov NCT01863706) but not all of the outcomes projected by methodological descriptions were reported as results in the study report (cases of diarrhoea, nausea and vomiting were not completely reported). Moreover, the study publication reports outcomes (hypotension, nausea, transfusion) not listed in the registered protocol
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by funding from the Hormozgan University of Medical Sciences (the institution of the authors)

Ramirez 2001

Methods	3-arm controlled randomised trial.
Participants	Between dates unspecified, an unspecified number of parturients were randomised in an unspecified setting and country. The population comprised primiparous women, with singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients that were multiparous, severely anaemic, and hypertensive conditions during pregnancy
Interventions	5 IU of oxytocin administered by an intravenous bolus versus 200 mcg ergometrine administered by an intravenous bolus vs placebo or control
Outcomes	The study recorded the following outcome: Change in Hb level
Notes	Contact with study authors for additional information: no. Additional data from authors: no. Abstract only available and data provided could not be used for meta-analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.

Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Methods of blinding were not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Objective assessment of blood loss	Unclear risk	Methods of evaluating blood loss were not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	Not reported.
Funding source	Unclear risk	Not reported.

Rashid 2009

Methods	2-arm active-controlled randomised trial.
Participants	Between January 2003 and December 2003, 686 parturients were randomised in a hospital setting in Saudi Arabia. The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing caesarean section or requiring oxytocin infusion in the third stage, or those with pre-eclampsia, cardiac disorder, hypertension on treatment, antepartum haemorrhage, pre-term labour (less than 37 weeks), post maturity (more than 42 weeks) or Hb less or equal to 90 g/L
Interventions	500 mcg plus 5 IU of ergometrine plus oxytocin administered intramuscularly (n = 340) versus 10 IU of oxytocin administered by an intravenous infusion (n = 346)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, manual removal of placenta, blood loss (mL), third-stage duration (min), nausea, vomiting headache
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Randomisation was achieved using computer-generated random numbers
Allocation concealment (selection bias)	Unclear risk	Investigators used sequentially-numbered, sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study participants and caregivers were not blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessors were not blinded to treatment allocations.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss "clinically in a standard way" by collection with a plastic sheet that was subsequently drained (with clots) into a graduated measuring jug, and by weighing swabs and towels. "Any delayed haemorrhage within 24 hours after delivery was calculated."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification, but not all of the outcomes projected by methodological descriptions were reported as results in the study report (cases of requirement for additional syntometrine [ergometrine plus oxytocin] were omitted)
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Ray 2001

Methods	2-arm active-controlled randomised trial.
Participants	Between dates unspecified, 200 parturients were randomised in a hospital setting in India. The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised

	parturients undergoing elective caesarean section, or those with pre-term labour (less than 32 weeks), prolonged labour, antepartum haemorrhage, pre-eclampsia, intrauterine death, multiple pregnancy, epilepsy, asthma, cardiac/kidney disorder, coagulopathy or anaemia
Interventions	400 mcg of misoprostol administered orally (n = 100) versus an unspecified dose of ergometrine administered by an unspecified injectable method (n = 100)
Outcomes	The study recorded the following outcomes: additional uterotonics, transfusion, manual removal of placenta, hypertension
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study participants and caregivers were blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Unclear risk	Investigators evaluated blood loss in the first 2 hours after delivery of the placenta, by "clinical estimation." However, blood loss data were not reported in a format that could be extracted for the purpose of this review
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification, but not all of the outcomes projected by methodological descriptions were reported as results in the study report
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the

		analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Reyes 2011a

Methods	2-arm active-controlled randomised trial.
Participants	Between August 2008 and August 2009, 144 parturients were randomised in a hospital setting in Panama. The population comprised women of parity 5 or more, a singleton pregnancy, at high risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing emergency caesarean section, or those with coagulopathy, unknown parity or known allergy to carbetocin
Interventions	100 mcg of carbetocin administered by an intravenous bolus (n = 45) versus 20 IU of oxytocin administered by an intravenous infusion (n = 90). There were 9 exclusions post randomisation but it was unclear from which group
Outcomes	The study recorded the following outcomes: additional uterotonics, transfusion, manual removal of placenta, breastfeeding, nausea, vomiting. Headache. Shivering. Abdominal pain
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Low risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding (of study participants and caregivers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessor blinding was not reported.
Objective assessment of blood loss	Unclear risk	Methods of evaluating blood loss were not reported.

Incomplete outcome data (attrition bias) All outcomes	Low risk	"Se pudieron reclutar 144 pacientes, en quienes se dio la aleatorización en dos grupos (carbetocina:oxitocina) en una pro-porción 1:2. Cualquier causal de falla en el seguimiento del protocolo establecido obli-gaba a la exclusión de la paciente del estudio
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification, but not all of the outcomes projected by methodological descriptions were reported as results in the study report (cases of PPH were omitted)
Intention to treat analysis	High risk	Not all study participants were included in the analysis.
Funding source	Unclear risk	Ferring Pharmaceuticals donated carbe-tocin. No other external funding was re-quired for the study

Reyes 2011b

Methods	2-arm active-controlled double-dummy randomised trial.
Participants	Between July 2010 and September 2010, 57 parturients were randomised in a hospital setting in Panama. The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by both caesarean and vaginal delivery. Exclusion criteria comprised parturients with HELLP syndrome, blood dyscrasia or multiple pregnancy
Interventions	100 mcg of carbetocin administered by an intravenous bolus (n = 26) versus 10 IU of oxytocin administered by an intravenous infusion (n = 29). There were 2 exclusions post randomisation but it was unclear from which group
Outcomes	The study recorded the following outcomes: additional uterotonics, transfusion, change in Hb level, third-stage duration (min), breastfeeding. Vomiting. Headache. Fever
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The randomisation was computer-gener-ated.

Allocation concealment (selection bias)	Unclear risk	Investigators used opaque, sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study was "double-blind": "because the 2 drugs are administered differently, a double dummy system for administration was used."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Unclear risk	Methods of evaluating blood loss were not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 women were excluded from the study analysis after randomisation ("1 given drug before expulsion of placenta; 1 ampoule of the drug broken before use")
Selective reporting (reporting bias)	High risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	High risk	Those who withdrew from the study after randomisation were not included in the analysis
Funding source	Low risk	Source(s) of funding for the study were not reported.

Rogers 1998

Methods	2-arm controlled randomised trial.
Participants	Between June 1993 and December 1995, 1512 parturients were randomised in a hospital setting in the UK. The population comprised women of parity 5 or less, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing augmentation of labour or instrumental delivery or requiring epidural analgesia, or those with placenta praevia, previous PPH, antepartum haemorrhage, Hb less than 100 g/L or mean corpuscular volume less than 75 fL, non-cephalic presentation, multiple pregnancy, intrauterine death, grand multiparity (more than 5), fibroids, anticoagulation therapy, pre-term labour (less than 32 weeks) or contraindications to any of the drugs
Interventions	An unspecified dose of ergometrine plus oxytocin administered by an unspecified route (n = 748) versus placebo or control (n = 764)

Rogers 1998 *(Continued)*

Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000.,Aaditional uterotonics, transfusion, manual removal of placenta, blood loss (mL), change in Hb level, third-stage duration (min), NNU admissions, breastfeeding, nausea, vomiting, headache
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation schedule used variably sized balanced blocks, and the randomisation envelopes were prepared in advance in the National Perinatal Epidemiology Unit (NEPU)
Allocation concealment (selection bias)	Low risk	Investigators used sequentially-numbered, opaque, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study participants and caregivers were not blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessors were not blinded to treatment allocations.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss by the estimation of attending midwives
Incomplete outcome data (attrition bias) All outcomes	Low risk	Blood loss data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by funding from the Public Health and Operational Research Committee of the Anglia and Oxford Regional Health Authority, UK (public funding)

Rosseland 2013

Methods	3-arm placebo-controlled randomised trial.
Participants	Between November 2009 and September 2011, 76 parturients were randomised in a hospital setting in Norway. The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by elective caesarean section. Exclusion criteria comprised parturients with pre-eclampsia, placenta praevia, placenta accreta, von Willebrand disease or other bleeding disorder or preoperative systolic arterial pressure less than 90 mmHg
Interventions	5 IU of oxytocin administered by an intravenous bolus (n = 26) versus 100 mcg of carbetocin administered by an intravenous bolus (n = 25) versus placebo or control (n = 25)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, blood loss (mL), change in Hb level, headache
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment was allocated by a computer-generated list of random numbers. The block size varied between 6 and 9, with stratification into 2 strata: BMI less than 30 and BMI of 30 or more
Allocation concealment (selection bias)	Low risk	Investigators used sequentially-numbered, opaque, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was "double-blinded": "to maintain blinding of the participants and investigators, the test medicine was delivered to the Department of Anaesthesiology in 10 mL syringes containing 5 mL of solution marked only with trial identification and randomisation numbers. The 10 mL syringes with the test medicines were prepared by a staff anaesthesiologist, who was otherwise uninvolved in the study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.

Objective assessment of blood loss	High risk	Investigators evaluated blood loss with the following formula: (0.75 x height in inches x 50) plus (weight in pounds x 50) x ((pre-delivery haematocrit measurement - post-delivery haematocrit measurement)/prede-livery haematocrit measurement)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Low risk	The study report matches the study protocol that was registered (ClinicalTrials.gov NCT00977769)
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	High risk	The study was supported by funding from Ferring Pharmaceuticals

Rozenberg 2015

Methods	2-arm placebo-controlled randomised trial.
Participants	Between dates unspecified, 1721 parturients were randomised in a hospital setting in France. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing emergency caesarean section, or those with known hypersensitivity to prostaglandins
Interventions	400 mcg plus 10 IU of misoprostol plus oxytocin administered orally plus by an intravenous bolus (n = 863) versus 10 IU of oxytocin administered by an intravenous bolus (n = 857)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, additional uterotonics, transfusion, death, fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study participants and caregivers were blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Unclear risk	Methods of evaluating blood loss were not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"The study excluded 57 women from the misoprostol group and 61 from the placebo group because they had caesareans." The study report did not specify whether exclusions occurred before or after randomisation
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	The authors excluded 119 study participants from the analysis because they experienced caesarean deliveries: it was unclear from the study report whether these exclusions occurred before or after randomisation
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Sadiq 2011

Methods	2-arm active-controlled randomised trial.
Participants	Between November 2009 and September 2011, 1865 parturients were randomised in a hospital setting in Nigeria. The population comprised women of parity 6 or less, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing instrumental delivery, or those with diabetes, noncephalic presentation, anaemia, antepartum haemorrhage, multiple pregnancy, grand multiparity (more than 6) or known allergy

Interventions	10 IU of oxytocin administered by an intravenous bolus (n = 900) versus 600 mcg of misoprostol administered orally (n = 900)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, blood loss (mL), change in Hb level
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random assignments were generated by dice-box.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study participants and caregivers were not blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessor blinding was not reported.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss at delivery by collection with pre-calibrated kidney dishes
Incomplete outcome data (attrition bias) All outcomes	Low risk	"46 of the administered questionnaires were invalidated leaving a total of 1819 valid questionnaires (912 for oxytocin and 907 for misoprostol). The data were further reduced through a process of computer randomisation so as to have [an] equal study population in the 2 medication groups: oxytocin group (900 subjects) and misoprostol group (900 subjects)"
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	High risk	Not all study participants were included in the analysis.
Funding source	Low risk	The study was supported by funding from the University of Maiduguri Teaching Hos-

		pital. Study medications were donated by Emzor Pharmaceutical Industries

Samimi 2013

Methods	2-arm active-controlled double-blinded randomised trial.
Participants	Between March 2011 and June 2011, 216 parturients were randomised in a hospital setting in Iran. The population comprised women of parity 4 or less, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients with hypertension, pre-eclampsia, uterine rupture, cervical tear, asthma, cardiovascular/renal/liver disorders, grand multiparity (not defined), fibroids or previous PPH
Interventions	100 mcg of carbetocin administered intramuscularly (n = 109) versus 200 mcg plus 5 IU of ergometrine plus oxytocin administered intramuscularly (n = 107)
Outcomes	The study recorded the following outcomes: morbidity, additional uterotonics, death,. change in Hb level, nausea, vomiting, tachycardia, hypotension, shivering, abdominal pain
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using a random number table.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients and medical personnel were blinded to the type of drug."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Unclear risk	Methods of evaluating blood loss were not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	At 24 hours postpartum, blood samples could not be collected from 16 women (9 in the carbetocin group and 7 in the ergometrine plus oxytocin group)

Selective reporting (reporting bias)	Low risk	The study report matches the study protocol that was registered (Iranian registry of clinical trials number 138810212854N2)
Intention to treat analysis	High risk	The authors excluded 16 study participants from the analysis because postpartum Hb measurements were not available
Funding source	Unclear risk	The study was supported by funding from the Kashan University of Medical Sciences (the institution of the authors)

Shrestha 2011

Methods	2-arm active-controlled randomised trial.
Participants	Between 1st September 2009 and 28th February 2010, 200 parturients were randomised in a hospital setting in Nepal. The population comprised women of unspecified parity, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients with polyhydramnios, chorioamnionitis, preterm labour, previous caesarean, asthma, cardiac disorder or contraindication/hypersensitivity to the use of prostaglandin and uterotonics
Interventions	1000 mcg of misoprostol administered rectally (n = 100) versus 10 IU of oxytocin administered intramuscularly (n = 100)
Outcomes	The study recorded the following outcomes: PPH at 500, morbidity, death, blood loss (mL), change in Hb level, third-stage duration (min), fever, abdominal pain
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment was randomly allocated as per the lottery technique
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study participants and caregivers were not blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.

Objective assessment of blood loss	Low risk	Investigators evaluated blood loss in the 48 hours postpartum, by collection with pre-weighed sterile pads and a calibrated bucket. All the soaked drapes and pads were weighed and the dry weights of these materials were subtracted to calculate blood loss on the basis that 1 g is equivalent to 1 mL
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Singh 2009

Methods	4-arm active-controlled double-dummy randomised trial.
Participants	Between dates unspecified, 300 parturients were randomised in a hospital setting in India. The population comprised women of unspecified parity, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing augmentation of labour, or those with intrauterine death, antepartum haemorrhage, multiple pregnancy, malpresentation, cardiac disorder, rhesus-negative mother, hypertension, Hb less than 70 g/L or hypersensitivity/contraindication to prostaglandins
Interventions	400 mcg or 600 mcg of misoprostol administered sublingually (n = 150) versus 5 IU of oxytocin administered by an intravenous bolus (n = 75) versus 200 mcg of ergometrine administered by an intravenous bolus (n = 75)
Outcomes	The study recorded the following outcomes: PPH at 500, additional uterotonics, transfusion, manual removal of placenta, blood loss (mL), third-stage duration (min), fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Drug packets were sealed and coded by the same individual using a computer-generated random number chart
Allocation concealment (selection bias)	Unclear risk	Investigators used sealed drug packets.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was "double-blind": active treatments and placebo treatments were "identical" and investigators were "thus blinded."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Low risk	Investigators removed any linen soiled with amniotic fluid, and placed a disposable and absorbent pre-weighed linen saver sheet with a pre-weighed polythene bag under the mother to collect blood from the uterine cavity. Any blood clots were expressed from the vagina into the polythene bag, which was then removed and weighed. A fresh pre-weighed sanitary napkin was applied. Separate swabs were not included in the final calculation (addition of the various gravimetric measurements), that was performed 1 hour after delivery. "The specific gravity of blood being 1.08, the amount of blood lost in mL was equal to the weight in grams."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification, but not all of the outcomes projected by methodological descriptions were reported as results in the study report (changes in Hb measurements were unspecified beyond textual summary that "all groups showed a slight decrease in mean haemoglobin concentration 24 hours postpartum [maximum decrease of 0.6 g/dL]; however, the difference was not significant [ANOVA, $P > 0.05$]")

Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Soltan 2007

Methods	4-arm active-controlled randomised trial.
Participants	Between April 2002 and February 2003, 1200 parturients were randomised in a hospital setting in Egypt. The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing caesarean section, or those with traumatic PPH, blood disorders, chorioamnionitis, placenta praevia or placental abruption
Interventions	200 mcg of ergometrine administered intramuscularly (n = 300) versus 600 mcg to 1000 mcg of misoprostol administered sublingually (n = 900)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, additional uterotonics, transfusion, manual removal of placenta, death, blood loss (mL), change in Hb level, third-stage duration (min), vomiting, fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation was computer-generated.
Allocation concealment (selection bias)	Low risk	Investigators used opaque, closed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study participants and caregivers were not blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessor blinding was not reported.

Soltan 2007 *(Continued)*

Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by collection with a graduated plastic bag, and by weighing towels, linen and gauzes
Incomplete outcome data (attrition bias) All outcomes	High risk	"144 women were excluded from analysis because they were exposed to trauma to the perineum, vagina or cervix during labour and had traumatic excessive bleeding."
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	High risk	Not all study participants were included in the analysis.
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Sood 2012

Methods	2-arm placebo-controlled randomised trial.
Participants	Between June 2003 and July 2005, 174 parturients were randomised in a hospital setting in India. The population comprised women of unspecified parity, either singleton or multiple pregnancy, at high risk for PPH, who delivered by either elective or emergency caesarean. Exclusion criteria were not specified
Interventions	400 mcg plus 20 IU of misoprostol plus oxytocin administered sublingually plus by an intravenous infusion (n = 90) versus 20 IU of oxytocin administered by an intravenous infusion (n = 84)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, blood loss (mL), change in Hb level, nausea, vomiting, fever, shivering
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved by computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Investigators used sequentially-numbered, opaque, sealed envelopes made at phar-

		macy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study participants and caregivers were blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	High risk	Investigators evaluated intraoperative blood loss by collection with suction apparatus and sterile drapes before irrigation, and by evaluating the blood in abdominal swabs and gauzes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Stanton 2013

Methods	2-arm cluster controlled randomised trial.
Participants	Between 21st April 2011 and 30th November 2012, 1586 parturients were randomised in a community setting in Ghana. The population comprised women of unspecified parity, either singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria were not specified
Interventions	10 IU of oxytocin administered intramuscularly (n = 689) versus placebo or control (n = 897)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, death
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The 52 CHOs were randomly allocated equally to either the intervention or the control group; this allocation was stratified by both district and distance (at least 10 km, or less than 10 km) to emergency obstetric care. The randomisation sequence was determined using Stata (version 12)
Allocation concealment (selection bias)	Unclear risk	.Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"The random allocation was not masked."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessors were not blinded to treatment allocations.
Objective assessment of blood loss	Low risk	Investigators evaluated postpartum blood loss by collection with a BRASS-V calibrated plastic drape placed under the mother, who was asked to remain recumbent for 1 hour following delivery of the baby, or for 2 hours if active bleeding persisted. "Fluids, urine, and faeces were excluded from the blood loss measure by sweeping them to the side and into a receptacle."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"7 and 9 enrolled women in the oxytocin and control arms, respectively, lacked a blood-loss measure."
Selective reporting (reporting bias)	Low risk	The study report matches the study protocol that was registered (ClinicalTrials.gov NCT01108289)
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by funding from the Bill and Melinda Gates Foundation (public funding)

Su 2009

Methods	2-arm active-controlled double-blinded randomised trial.
Participants	Between January 2005 and April 2008, 370 parturients were randomised in a hospital setting in Singapore. The population comprised women of unspecified parity, a single-ton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing elective caesarean section, or those with multiple pregnancy, previous PPH, coagulopathy, coronary artery disease, hypertension or hypersensitivity/contraindications for the use of Syntometrine or carbetocin
Interventions	100 mcg of carbetocin administered intramuscularly (n = 185) versus 500 mcg plus 5 IU of ergometrine plus oxytocin administered intramuscularly (n = 185)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, manual removal of placenta, blood loss (mL), third-stage duration (min), nausea, vomiting, headache, shivering, abdominal pain
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was blocked and stratified by parity. The randomisation list with the allocation of the mode of intervention was forwarded from the Biostatistics Unit to the Department of Pharmacy at National University Hospital, where the purchased medications were kept
Allocation concealment (selection bias)	Low risk	Investigators used opaque packages made at pharmacy.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The identities of the medications were not known to the midwives, obstetricians and the participants. The medication codes were only broken following completion of the trial."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss by the visual estimation of attending obstetricians and midwives

Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Low risk	The study protocol was registered 2 years after beginning recruitment (ClinicalTrial. gov NCT00499005)
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by funding from the National Healthcare Group of Singapore (public funding)

Sultana 2007

Methods	2-arm active-controlled randomised trial.
Participants	Between January 2003 and December 2003, 400 parturients were randomised in a hospital setting in Bangladesh. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients with previous caesarean
Interventions	400 mcg of misoprostol administered orally (n = 210) versus 10 IU of oxytocin administered intramuscularly (n = 190)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, manual removal of placenta, shivering, abdominal pain
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and caregivers) was not reported

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss by the estimation of attending physicians after collection in a plastic bowl
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Surbek 1999

Methods	2-arm placebo-controlled randomised trial.
Participants	Between May 1997 and April 1998, 65 parturients were randomised in a Hospital setting in Switzerland. The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing caesarean section, or those with multiple pregnancy, pre-eclampsia, previous PPH or antepartum haemorrhage
Interventions	600 mcg of misoprostol administered orally (n = 31) versus placebo or control (n = 34)
Outcomes	The study recorded the following outcomes: PPH at 500, additional uterotonics, blood loss (mL), change in Hb level, third-stage duration (min), NNU admissions, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using random tables.

Surbek 1999 (*Continued*)

Allocation concealment (selection bias)	Low risk	Randomisation was performed by the pharmacy.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was "double-masked": "for proper masking, the study drugs were prepared by the hospital pharmacy as 3 identical gelatine capsules."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss by the estimation of attending physicians
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification, but not all of the outcomes projected by methodological descriptions were reported as results in the study report
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Tewatia 2014

Methods	2-arm active-controlled randomised trial.
Participants	Between March 2010 and February 2011, 100 parturients were randomised in a hospital setting in India. The population comprised women of parity 4 or less, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients with grand multiparity (more than 4), anaemia, malpresentation, polyhydramnios, antepartum haemorrhage, liver/renal disorder, previous caesarean, previous PPH, uterine anomaly, traumatic PPH or contraindications to use misoprostol or oxytocin
Interventions	10 IU of oxytocin administered by an intravenous infusion (n = 50) versus 600 mcg of misoprostol administered sublingually (n = 50)

Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, additional uterotonics, transfusion, death, blood loss (mL), change in Hb level, third-stage duration (min), nausea, vomiting. fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	.Randomisation was achieved using a computer-generated random number sequence
Allocation concealment (selection bias)	Unclear risk	Investigators used sequentially-numbered, opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Due to [the] nature of administration of the drugs, [the] patient or clinical care team could not be blinded. However, [the] statistician was unaware of the group allocation."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Low risk	Investigators removed any linen soiled with amniotic fluid, and placed a calibrated plastic bag under the mother to collect blood from the uterine cavity. After delivery of the placenta, a pre-weighed pad was placed high up in vagina until 1 hour afterwards. In cases of episiotomy, a separate pad was applied to the episiotomy site, and the fluid collected by this pad was not included in blood loss measurements
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised

Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Thilaganathan 1993

Methods	2-arm controlled randomised trial.
Participants	Between January 1988 and February 1990, 193 parturients were randomised in a hospital setting in the UK. The population comprised women of parity 4 or less, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing induction or augmentation of labour or instrumental delivery, or those with grand multiparity (not defined), malpresentation, multiple pregnancy, previous caesarean, previous PPH, antepartum haemorrhage, hypertension in pregnancy, intrauterine death, preterm rupture of membranes, cervical lacerations or third degree perineal tears
Interventions	Placebo or control (n = 90) versus 500 mcg plus 5 IU of ergometrine plus oxytocin administered intramuscularly (n = 103)
Outcomes	The study recorded the following outcomes: additional uterotonics, transfusion, manual removal of placenta, blood loss (mL), change in Hb level, third-stage duration (min)
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment was randomly allocated using standard randomisation tables
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study participants and caregivers were not blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss by the estimation of attending physicians
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants

Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	The study was conducted without external funding.

Ugwu 2014

Methods	2-arm active-controlled randomised trial.
Participants	Between 21st April 2011 and 31st March 2012, 120 parturients were randomised in a hospital setting in Nigeria. The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by either elective or emergency caesarean. Exclusion criteria comprised parturients requiring general anaesthesia, or those with multiple pregnancy, placenta praevia, pre-eclampsia, eclampsia, undiagnosed vaginal bleeding, prolonged labour, prolonged obstructed labour, cardiac/renal/ liver disorders or fever
Interventions	400 mcg plus 20 IU of misoprostol plus oxytocin administered sublingually plus by an intravenous infusion (n = 60) versus 20 IU of oxytocin administered by an intravenous infusion (n = 60)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, additional uterotonics, transfusion, death, blood loss (mL), change in Hb level, fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment allocations were generated by random tables.
Allocation concealment (selection bias)	Low risk	Investigators used sequentially-numbered, opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"There were no look-alike placebo tablets for women who had oxytocin alone... The obstetricians and the scrub nurses were unaware of which oxytocic was given to each patient, as they were screened off during the

		surgery... No member of the obstetric team had knowledge of which agent the patient received"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"There were no look-alike placebo tablets for women who had oxytocin alone... The obstetricians and the scrub nurses were unaware of which oxytocic was given to each patient, as they were screened off during the surgery... No member of the obstetric team had knowledge of which agent the patient received"
Objective assessment of blood loss	Low risk	Investigators evaluated intraoperative and postoperative blood loss by collection in a suction bottle. Furthermore, soiled drapes, abdominal packs and pieces of gauze were weighed and the known dry weights subtracted. Finally, vulva pads applied during the 4 hours post-operation, were also weighed and the known dry weights subtracted. Measurements obtained by these 3 methods were added together. Weight measurements were performed with a weighing scale made in China, of total weighing capacity of 5 kg and graduations of 0.25 g. Investigators considered that 1 g is equivalent to 1 mL of blood
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification, but not all of the outcomes projected by methodological descriptions were reported as results in the study report (cases of nausea, vomiting, diarrhoea, headaches, fatigue, dizziness, chills, flatulence and abdominal pain were omitted)
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Un Nisa 2012

Methods	2-arm active-controlled randomised trial.
Participants	Between 1st January 2012 and 30th June 2012, 100 parturients were randomised in a hospital setting in India. The population comprised women of parity 2 to 4, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients with previous PPH, multiple pregnancy, previous caesarean, macrosomia, pre-eclampsia, diabetes, cardiac/lung/bleeding/clotting disorders or taking anticoagulants
Interventions	10 IU of oxytocin administered by an intravenous bolus (n = 50) versus 500 mcg plus 5 IU of ergometrine plus oxytocin administered intramuscularly (n = 50)
Outcomes	The study recorded the following outcome: PPH at 500.
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study participants (patients) were divided by a lottery system in the 2 groups, each group comprising 50 patients
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study participants and caregivers were not blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss after the delivery of baby "by squeezing the soaked pads and quantifying the amount of blood clots in a kidney tray of standard size to be equal to 500 mL."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly al-

		located to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Uncu 2015

Methods	5-arm controlled randomised trial.
Participants	Between dates unspecified, 248 parturients were randomised in a hospital setting in Turkey. The population comprised women of parity 5 or less, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing caesarean section, or those with placenta praevia, previous PPH, antepartum haemorrhage, non-cephalic presentation, multiple pregnancy, intrauterine death, grand multiparity (more than 5), fibroids, pre-eclampsia or anticoagulation therapy
Interventions	Placebo or control (n = 49) versus 400 mcg to 800 mcg of misoprostol administered orally, vaginally or rectally (n = 199)
Outcomes	The study recorded the following outcomes: additional uterotonics, transfusion, third-stage duration (min), shivering, abdominal pain
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was generated by random tables.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and caregivers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Unclear risk	Methods of evaluating blood loss were not reported.

Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Vagge 2014

Methods	2-arm active-controlled randomised trial.
Participants	Between dates unspecified, 200 parturients were randomised in a hospital setting in India. The population comprised women of parity 4 or less, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing caesarean section, or those with cardiac disorder in pregnancy, uterine tumour in pregnancy, secondary PPH, grand multiparity (not defined), multiple pregnancy, polyhydramnios, anaemia, coagulopathy, antepartum haemorrhage, previous PPH, prolonged labour, precipitate labour or known allergic or hypersensitivity reaction to prostaglandins
Interventions	10 IU of oxytocin administered by an intravenous infusion (n = 100) versus 800 mcg of misoprostol administered rectally (n = 100)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, blood loss (mL), nausea, fever, shivering
Notes	Contact with study authors for additional information: no. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Investigators used simple random sampling.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study participants and caregivers were not blinded to treatment allocations

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Unclear risk	Methods of evaluating blood loss were not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Vaid 2009

Methods	3-arm active-controlled randomised trial.
Participants	Over 10 months between dates unspecified, 200 parturients were randomised in a hospital setting in India. The population comprised women of parity 4 or less, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients with grand multiparity (more than 4), multiple pregnancy, preterm labour (less than 32 weeks), HELLP syndrome, polyhydramnios, coagulopathy, asthma, cardiac/renal disorder, epilepsy, hypertension, Hb less than 80 g/L or known drug allergy
Interventions	400 mcg of misoprostol administered sublingually (n = 66) versus 200 mcg of ergometrine administered intramuscularly (n = 67)
Outcomes	The study recorded the following outcomes: PPH at 500, Additional uterotonics, transfusion, manual removal of placenta, nausea, vomiting, fever, shivering, abdominal pain
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment was allocated by a computer-generated random number

Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and care-givers) was unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Low risk	After the drainage of amniotic fluid, investigators evaluated blood loss by collection with a sterile calibrated BRASS-V drape placed under the mother. The drape remained in place for 1 hour. Furthermore, "blood loss in gauze pieces was calculated by subtracting the weight of dry gauze from the weight of blood-soaked gauze pieces."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Verma 2006

Methods	2-arm active-controlled double-dummy randomised trial.
Participants	Between 2005 and 2006, 200 parturients were randomised in a hospital setting in India. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria were not specified
Interventions	400 mcg of misoprostol administered sublingually (n = 100) versus 200 mcg of ergometrine administered intramuscularly (n = 100)
Outcomes	The study recorded the following outcomes: PPH at 500, additional uterotonics, manual removal of placenta, blood loss (mL), change in Hb level, third-stage duration (min), nausea, fever, shivering

Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was "double-blind": active treatments and placebo treatments were "identical-looking."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss "accurately with a specially designed calibrated blood collection drape (BRASS-V drape)."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	It was unclear from the study report whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were unclear.

Vimala 2004

Methods	2-arm active-controlled randomised trial.
Participants	Between October 2002 and January 2003, 120 parturients were randomised in a hospital setting in India. The population comprised women of parity 5 or less, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing induction or augmentation of labour or caesarean section, or those with preterm labour (less than 37 weeks), grand multiparity (more

	than 5), multiple pregnancy, hypertension in pregnancy, Hb less than 80 g/L or known hypersensitivity to prostaglandins
Interventions	400 mcg of misoprostol administered sublingually (n = 60) versus 200 mcg of ergometrine administered by an intravenous bolus (n = 60)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, manual removal of placenta, blood loss (mL), change in Hb level, third-stage duration (min), nausea, vomiting, headache, fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment was allocated by random tables.
Allocation concealment (selection bias)	Low risk	Investigators used sequentially-numbered, opaque, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Treatments were administered via different routes and the authors did not report any double dummy
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss by the estimation of attending nurses and obstetricians. After delivery of the baby, amniotic fluid was allowed to drain away, and amniotic fluid-soaked bed linens were covered with dry disposable 'linen-savers'. A wedge-shaped plastic bedpan was placed under the mother for 1 hour. Blood and clots from the bedpan were decanted into a measuring cylinder and measured. Blood-soaked swabs and linen-savers were weighed; the known dry weights were subtracted, for the weight of blood contained within them to be added to the value indicated by the measuring cylinder
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data

Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Vimala 2006

Methods	2-arm active-controlled randomised trial.
Participants	Between August 2004 and April 2005, 100 parturients were randomised in a hospital setting in India. The population comprised women of unspecified parity, a singleton pregnancy, at high risk for PPH, who delivered by either elective or emergency caesarean. Exclusion criteria comprised parturients with multiple pregnancy, antepartum haemorrhage, polyhydramnios, prolonged labour (more than 12 hours), previous more than 1 caesarean, previous uterine rupture, cardiac/liver/renal disorder, coagulopathy or Hb less than 80 g/L
Interventions	400 mcg of misoprostol administered sublingually (n = 50) versus 20 IU of oxytocin administered by an intravenous infusion (n = 50)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, blood loss (mL), change in Hb level, vomiting, headache, fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Investigators used opaque, sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study participants and caregivers were not blinded to treatment allocations

Vimala 2006 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Low risk	Investigators evaluated blood loss intraoperatively and in the first hour postoperatively "in a standard manner." They measured the volume of blood in the suction bottle, and weighed blood-soaked sponges and linen savers. Then they added the difference between dry and blood-soaked weights of sponges and linen savers, to the volume measured in the suction bottle
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were collected completely from all randomised study participants
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by funding from the Division of Reproductive Health and Nutrition, Indian Council of Medical Research (public funding)

Walley 2000

Methods	2-arm active-controlled double-dummy randomised trial.
Participants	Between 15th June 1998 and 15th May 1999, 401 parturients were randomised in a hospital setting in Ghana. The population comprised women of parity 5 or less, a singleton pregnancy, at low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing induction or augmentation of labour or caesarean section, or those with grand multiparity (more than 5), multiple pregnancy, preterm labour (less than 32 weeks), hypertension in pregnancy, HELLP syndrome, polyhydramnios, previous PPH, coagulopathy, precipitate labour, chorioamnionitis, Hb less than 80 g/L or a known hypersensitivity to prostaglandins
Interventions	400 mcg of misoprostol administered orally (n = 203) versus 10 IU of oxytocin administered intramuscularly (n = 198)

Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, manual removal of placenta, death, blood loss (mL), Change in Hb level, third-stage duration (min), nausea, vomiting, fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Investigators used sequentially-numbered, opaque packets made by administrative staff
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The identity of the placebo and active medications were concealed from caregivers and participants."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	High risk	Investigators evaluated blood loss by the estimation of attending physicians
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of those women randomised, blood loss measurements were unavailable in 3 cases, and postpartum Hb samples were unavailable in 9 cases
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Low risk	All those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by funding from MaterCare International and the Canadian International Development Agency (public funding)

Whigham 2014 *(Continued)*

Methods	2-arm active-controlled double-blinded randomised trial.
Participants	Between dates unspecified, 58 parturients were randomised in a hospital setting in Australia. The population comprised women of unspecified parity, either singleton or multiple pregnancy, at high risk for PPH, who delivered by emergency caesarean section. Exclusion criteria comprised parturients undergoing elective caesarean section or requiring general anaesthesia, or those with vascular/liver/renal disorders, preterm labour (less than 37 weeks), placenta praevia, placental abruption, previous more than 2 caesareans or an adverse reaction to carbetocin/oxytocin
Interventions	100 mcg of carbetocin administered by an intravenous bolus (n = 30) versus 5 IU of oxytocin administered by an intravenous bolus (n = 28)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, blood loss (mL), change in Hb level
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Investigators used computer-generated randomisation at pharmacy level, and none of the operating or anaesthetic doctors had access to this
Allocation concealment (selection bias)	Low risk	Randomisation was performed by the pharmacy.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was "double-blinded": women received "a blinded bolus of carbetocin" or "a blinded oxytocin bolus."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Low risk	Investigators evaluated intra-operative blood loss by the estimation of attending physicians. Excess blood was collected in measuring container by suction, and weighed together with any swabs soaked in blood
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data

Selective reporting (reporting bias)	Low risk	The study report matches the study protocol that was registered prospectively (AC-TRN 12612000466842)
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Low risk	The study was supported by funding from Frankston Hospital (the institution of the authors)

Yuen 1995

Methods	2-arm active-controlled double-blinded randomised trial.
Participants	Between February 1993 and March 1993, 1000 parturients were randomised in a hospital setting in Hong Kong. The population comprised women of unspecified parity, a singleton pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients requiring oxytocin infusion in the third stage, or those with pre-eclampsia or cardiac disorder
Interventions	500 mcg plus 5 IU of ergometrine plus oxytocin administered intramuscularly (n = 496) versus 10 IU of oxytocin administered intramuscularly (n = 495)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, morbidity, additional uterotonics, transfusion, manual removal of placenta, death, change in Hb level, nausea, vomiting, headache
Notes	Contact with study authors for additional information: yes. Additional data from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using computer-generated random numbers
Allocation concealment (selection bias)	Unclear risk	Investigators used sequentially-numbered, opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"When a patient entered the study, a nursing officer who was not involved in the management of the patient drew up the indicated medication and handed this to

		the patient's attendants." Study participants and caregivers were thus blinded to treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Objective assessment of blood loss	Unclear risk	Investigators evaluated blood loss during delivery "by measuring the amount of blood clots and weighing the towels used."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"9 [randomised participants] were excluded: 3 had a twin pregnancy, 1 had blood transfusion during labour, and the other 5 had unavailable records."
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	High risk	Not all study participants were included in the analysis.
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

Zachariah 2006

Methods	3-arm active-controlled randomised trial.
Participants	Over 8 months between dates unspecified, 2023 parturients were randomised in a hospital setting in India. The population comprised women of unspecified parity, unspecified whether singleton or multiple pregnancy, at both high and low risk for PPH, who delivered by vaginal delivery. Exclusion criteria comprised parturients undergoing caesarean section, or those with asthma, cardiac disorder, rhesus factor incompatibility or hypertension
Interventions	400 mcg of misoprostol administered orally (n = 730) versus 10 IU of oxytocin administered intramuscularly (n = 617) versus 200 mcg of ergometrine administered by an intravenous bolus (n = 676)
Outcomes	The study recorded the following outcomes: PPH at 500, PPH at 1000, additional uterotonics, transfusion, manual removal of placenta, death, blood loss (mL), change in Hb level, third-stage duration (min), nausea, vomiting, headache, fever, shivering
Notes	Contact with study authors for additional information: yes. Additional data from authors: yes

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using computer-generated random numbers
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding (of study participants and caregivers) was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not reported.
Objective assessment of blood loss	Low risk	After the drainage of amniotic fluid, investigators evaluated blood loss by collection with a large sterile plastic bag placed under the mother until she was transferred to the postnatal department. The blood collected in the plastic bag was then transferred to a measuring jar. Mops were not used in the labour room, and gauze pieces were counted
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not mention any incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Intention to treat analysis	Unclear risk	The authors did not specify whether all those who were enrolled and randomly allocated to treatment were included in the analysis, in the groups to which they were randomised
Funding source	Unclear risk	Source(s) of funding for the study were not reported.

ACTRN, Australian Clinical Trials Registration Number; **ANOVA**, one-way Analysis Of Variance; **ASA I or II**, ASA Physical Status Classification System: ASA I represents a normal healthy patient, ASA II represents a patient with mild systemic disease; **BMI**, Body Mass Index; **cc**, cubic centimetres; **CHOs**, community health officers; **cm**, centimetres; **CTRI**, Clinical Trials Registry of India; **DIC**, Disseminated Intravascular Coagulopathy; **dL**, decilitres; **EudraCT**, European Clinical Trials database; **fL**, femtolitres (measurement of mean corpuscular volume); **g**, grams; **Hb**, Haemoglobin; **HELLP syndrome**, Hemolysis (destruction of red blood cells), Elevated Liver enzymes (which indicate liver damage), and Low Platelet count; **HIV**, Human Immunodeficiency Virus; **Hong Kong SAR**,

Hong Kong Special Adminstrative Region; **IU**, International Units; **kg**, kilograms; **km**, kilometres; **L**, litres; **mcg**, micrograms; **mg**, milligrams; **min**, minutes; **mL**, millilitres; **mmHG**, millimetres of mercury (unit of pressure); **mmol**, millimoles; **NCT**, National Clinical Trial (number); **NEPU**, National Perinatal Epidemiology Unit; **NHS**, National Health Service; **nm**, nanometres; **NNU**, Neonatal Unit; **PACTR**, Pan African Clinical Trials Registry; **PPH**, Postpartum Haemorrhage; **PROM**, Premature Rupture Of Membranes; **RCOG**, Royal College of Obstetricians and Gynaecologists; **UK**, United Kingdom; **UNDP/UNFPA**, United Nations Development Programme/United Nations Population Fund; **USA**, United States of America; **WHO**, World Health Organization.

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

Study	Reason for exclusion
Abdel-Aleem 1993	Not eligible intervention
Abdel-Aleem 1997	Not eligible intervention
Abdel-Aleem 2013	Not eligible intervention
Abdollahy 2000	Not eligible intervention
Al-Harazi 2009	Same drug intervention both arms and only different route of misoprostol administration
Anandakrishnan 2013	Same drug intervention both arms and only different dose of carbetocin administration
Anjaneyulu 1988	Not eligible intervention
Anvaripour 2013	Intervention given after the third stage of labour
Athavale 1991	Not eligible intervention
Ayedi 2011a	Same drug intervention both arms and only different dose of oxytocin administration
Ayedi 2011b	Not eligible intervention
Aziz 2014	Quasi-randomised
Bader 2000	Not eligible intervention
Badhwar 1991	Not eligible intervention
Bai 2014	Not eligible uterotonic
Balki 2006	Same drug intervention both arms and only different dose of oxytocin administration
Banovska 2013	Not eligible intervention
Barbaro 1961	Not eligible intervention

(Continued)

Baumgarten 1983	Not eligible uterotonic
Bhattacharya 1988	Not eligible uterotonic
Bhavana 2013	Not eligible intervention
Bider 1991	Not eligible intervention
Bider 1992	Not eligible intervention
Bisri 2011	Same drug intervention both arms and only different route of oxytocin administration
Biswas 2007	Not eligible uterotonic
Bivins 1993	Not eligible uterotonic
Blum 2010	Intervention for treatment of PPH
Bonham 1963	Quasi-randomised
Bonis 2012	Quasi-randomised
Cappiello 2006	Not eligible intervention
Carvalho 2004	Same drug intervention both arms and only different dose of oxytocin administration
Catanzarite 1990	Not eligible intervention
Chaplin 2009	Not eligible intervention
Chaudhuri 2014	Inappropriate population (excluded women who had PPH)
Chestnut 1987	Not eligible intervention
Chou 1994	Not eligible intervention
Chua 1995	Not eligible intervention
Chukudebelu 1963	Quasi-randomised
Cooper 2004	Same drug intervention both arms and only different dose of oxytocin administration
Cordovani 2012	Same drug intervention both arms and only different dose of carbetocin administration
Dagdeviren 2014	Same drug intervention both arms and only different route of oxytocin administration
Dahiya 1995	Not eligible intervention

Daley 1951	Quasi-randomised
Daly 1999	Inappropriate population
Dao 2009	Intervention for treatment of PPH
Davies 2005	Same drug intervention both arms and only different route of oxytocin administration
De bonis 2012	Quasi-randomised
Dennehy 1998	Same drug intervention both arms and only different route of oxytocin administration
Devi 1988	Not eligible intervention
Diab 1999	Quasi-randomised
Dickinson 2009	Not eligible population (terminations 2nd trimester)
Dommisse 1980	Not randomised
Dong 2011	Not eligible intervention
Durocher 2012	Quasi-randomised
Dutta 2000	Quasi-randomised
Dweck 2000	Not eligible intervention
Dzuba 2012	Same drug intervention both arms and only different route of oxytocin administration
Elati 2011	Same drug intervention both arms and only different route of misoprostol administration
Erkkola 1984	Not eligible intervention
Farber 2013	Not eligible intervention
Farber 2015	Not eligible intervention
Fatemeh 2011	Same drug intervention both arms and only different route of oxytocin administration
Fawzy 2012	Treatment (not prevention) of PPH.
Forster 1957	Quasi-randomised
Francis 1965	Quasi-randomised
Friedman 1957	Quasi-randomised

Fugo 1958	Quasi-randomised
Gai 2004	Not eligible intervention
George 2010	Same drug intervention both arms and only different route of oxytocin administration
Ghulmiyyah 2007	Not eligible intervention
Gobbur 2011	Not eligible intervention
Gohel 2007	Not eligible intervention
Goswami 2013	Not eligible intervention
Groeber 1960	Not eligible intervention
Gungorduk 2010a	Same drug intervention both arms and only different route of oxytocin administration
Gungorduk 2010b	Not eligible intervention
Gungorduk 2011	Not eligible intervention
Gungorduk 2013	Not eligible intervention
Gupta 2014	Not eligible intervention
Habek 2007	Not eligible intervention
Hacker 1979	Not randomised
Halder 2013	Not eligible intervention
Hoffman 2006	Not appropriate intervention (comparing timing of oxytocin)
Hofmeyr 2004	Intervention for treating PPH
Howard 1964	Not eligible intervention
Huh 2004	Same drug intervention both arms and only different route of oxytocin administration
Hunt 2013	Not eligible intervention
Häivä 1994	Quasi-randomised
Ilancheran 1990	Not randomised
Irons 1994	Inappropriate population (excluded women who had PPH)

Jackson 2001	Not appropriate intervention (comparing timing of oxytocin)
Jiang 2001	Same drug intervention both arms and only different route of oxytocin administration
Jin 2000	Not eligible intervention
Jolivet 1978	Not eligible intervention (given oral ergometrine for 6 days)
Jonsson 2010	Same drug intervention both arms and only different route of oxytocin administration
Kashanian 2010	Ineligible population (excluded women with PPH)
Kemp 1963	Quasi-randomised
Khan 1997	Not eligible intervention
Khan 2003	Same drug intervention both arms and only different route of misoprostol administration
Khan 2012	Same drug intervention both arms and only different route of oxytocin administration
Khanun 2011	Same drug intervention both arms and only different route of misoprostol administration
Khurshid 2010	Not eligible intervention
Kikutani 2003a	Innapropriate population
Kikutani 2003b	Innapropriate population
King 2010	Same drug intervention both arms and only different route of oxytocin administration
Kintu 2012	Same drug intervention both arms and only different dose of oxytocin administration
Kiran 2012	Same drug intervention both arms and only different dose of oxytocin administration
Kore 2000	Not eligible intervention
Kovacheva 2015	Same drug intervention both arms and only different route of oxytocin administration
Kovavisarach 1998	Not eligible intervention
Kumar 2011	Not eligible intervention (carboprost)
Kushtagi 2006	Not eligible intervention (carboprost)
Lamont 2001	Not eligible intervention (carboprost)

Le 2000	Not eligible intervention
Leader 2002	Not eligible population (2nd trimester)
Li 2002	Not eligible intervention
Li 2003	Not eligible intervention
Li 2011	Not eligible intervention
Lin 2009	Not eligible intervention
Liu 1997	Not eligible intervention
Liu 2002	Not eligible intervention
Luamprapas 1994	Not eligible intervention
Mangla 2012	Not eligible intervention
Mankuta 2006	Not eligible intervention
Mansouri 2011	Same drug intervention both arms and only different route of misoprostol administration
Martinez 2006	Not eligible intervention
McGinty 1956	Quasi-randomised
Miller 2009	Not eligible intervention
Mirghafourvand 2015	Not eligible intervention
Mollitt 2009	Same drug intervention both arms and only different route of oxytocin administration
Moore 1956	Same drug intervention both arms and only different type of the same drug
Movafegh 2011	Not eligible intervention
Muller 1996	Not randomised
Munishankarappa 2009	Same drug intervention both arms and only different route of oxytocin administration
Munn 2001	Same drug intervention both arms and only different route of oxytocin administration
Murphy 2009	Same drug intervention both arms and only different route of oxytocin administration

Nankali 2013	Not eligible intervention
NCT01710566 2012	Study withdrawn
Nellore 2006	Not eligible intervention
Nelson 1983	Not eligible intervention
Newton 1961	Quasi-randomised
Nguyen-Lu 2013	Same drug intervention both arms and only different dose of carbetocin administration
Nieminen 1964	Not eligible intervention
Norchi 1988	Not eligible intervention
Oberbaum 2005	Not eligible intervention
Oguz 2014	Same drug intervention both arms and only different route and timing of oxytocin administration
Ozalp 2010	Not eligible intervention
Ozcan 1996	Not eligible intervention
Ozkaya 2005	Inappropriate population (excluded women who had PPH)
Padhy 2006	Not eligible intervention
Palacio 2011	Same drug intervention both arms and only different dose of oxytocin administration
Paull 1977	Same drug intervention both arms and only different doses of drug administration
Pei 1996	Not randomised
Perdiou 2009	Not eligible intervention
Phromboot 2010	Not eligible intervention
Pierre 1992	Quasi-randomised
Pinder 2002	Same drug intervention both arms and only different doses of drug administration
Pisani 2012	Quasi-randomised
Poeschmann 1991	Quasi-randomised
Porter 1991	Not eligible intervention

Priya 2015	Inappropriate population (measured blood loss after the delivery of the placenta)
Puri 2012	Not eligible intervention
Qiu 1999	Not eligible population (2nd stage)
Quiroga 2009	Not eligible intervention
Rajwani 2000	Not eligible intervention
Reddy 1989	Not eligible intervention
Reddy 2001	Not eligible intervention
Rooney 1985	Quasi-randomised
Rosales-Ortiz 2013	Quasi-randomised
Rouse 2011	Same drug intervention both arms and only different doses of drug administration
Sadeghipour 2013	Not eligible intervention
Saito 2007	Qausi-randomised
Samuels 2005	Not eligible intervention
Sariganont 1999	Not randomised
Sarna 1997	Same drug intervention both arms and only different doses of drug administration
Sartain 2008	Same drug intervention both arms and only different doses of drug administration
Schaefer 2004	Same drug intervention both arms and only different timings of drug administration
Schemmer 2001	Same drug intervention both arms and only different timings of drug administration
Sekhavat 2009	Not eligible intervention
Sentilhes 2014	Not eligible intervention
Senturk 2013	Not eligible intervention
Shahid 2013	Not eligible intervention
Sharma 2014	Not randomised

Sheehan 2011	Same drug intervention both arms and only different doses of drug administration
Shirazi 2013	Not eligible intervention
Shrestha 2007	Not eligible intervention
Singh 2005	Not eligible intervention
Siriwarakul 1991	Not eligible intervention
Soiva 1964	Quasi-randomised
Sorbe 1978	Quasi-randomised
Soriano 1995	Quasi-randomised
Stearn 1963	Quasi-randomised
Svanstrom 2008	Innapropriate population
Symes 1984	Innapropriate population
Taj 2014	Not eligible intervention
Takagi 1976	Not eligible intervention
Tanir 2009	Not eligible intervention
Tarabrin 2012	Not eligible intervention
Tariq 2015b	Administered for treatment of PPH
Tehseen 2008	Not eligible intervention
Terry 1970	Not eligible intervention
Tessier 2000	Same drug intervention both arms and only different doses of drug administration
Tharakan 2008	Same drug intervention both arms and only different doses of drug administration
Thomas 2007	Same drug intervention both arms and only different doses of drug administration
Thornton 1988	Quasi-randomised
Tita 2012	Same drug intervention both arms and only different doses of drug administration

Tripti 2006	Not eligible intervention
Tripti 2009	Not randomised
Tudor 2006	Not eligible intervention
Van den Enden 2009	Same drug intervention both arms and only different doses of drug administration
Van Selm 1995	Not eligible uterotonic
Vasegh 2005	Quasi-randomised
Vaughan 1974	Innapropriate population
Ventoskovskiy 1990	Not eligible intervention
Verghese 2008	Not eligible intervention
Vogel 2004	Not eligible outcomes
Wallace 2008	Same drug intervention both arms and only different regimen of oxytocin administration
Walraven 2005	Not eligible uterotonic (oral ergometrine)
Wang 2000	Not eligible intervention
Weeks 2013	Self-administered drug
Weihong 1998	Not eligible intervention
Weiss 1975	Not eligible outcomes
Wetta 2013	Same drug intervention both arms and only different doses of drug administration
Winikoff 2012	Same drug intervention both arms and only different doses of drug administration
Wong 2006	Same drug intervention both arms and only different doses of drug administration
Wright 2006	Not eligible intervention
Wu 2007	Not eligible intervention
Xu 2003	Not eligible intervention
Xu 2013	Not eligible intervention

Yamaguchi 2011	Same drug intervention both arms and only different doses of drug administration
Yan 2000	Not eligible intervention
Yang 2001	Not eligible intervention
Young 1988	Not eligible intervention
Zamora 1999	Not eligible intervention
Zaporozhan 2013	Not eligible intervention
Zhao 1998	Not eligible intervention
Zhao 2003	Not eligible intervention
Zhou 1994	Same drug intervention both arms and only different doses of drug administration

PPH: postpartum haemorrhage

Characteristics of studies awaiting assessment *[ordered by study ID]*

Adanikin 2013

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Adhikari 2007

Methods	
Participants	
Interventions	
Outcomes	

Notes	

Ahmed 2015

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Akinaga 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Ali 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Alli 2013

Methods	
Participants	
Interventions	
Outcomes	

Notes	

Alwani 2014

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Ashwal 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Asmat 2017

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Ayedi 2012

Methods	
Participants	
Interventions	
Outcomes	

Ayedi 2012 (*Continued*)

Notes	

Baig 2015

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Begum 2015

Methods	Randomised trial.
Participants	100 women with singleton term pregnancy undergoing caesarean with spinal anaesthesia
Interventions	20 IU of oxytocin administered by an intravenous infusion or 400 mcg of misoprostol administered sublingually
Outcomes	Additional uterotonics, blood loss (mL), change in Hb level, fever,.shivering
Notes	Method of randomisation not clear and 'Risk of bias' assessment is uncertain. Abstract only. Unable to contact authors

Beigi 2009

Methods	Randomised trial.
Participants	542 nulliparous pregnant women
Interventions	20 IU of oxytocin administered intravenously or 400 mcg of misoprostol administered sublingually
Outcomes	PPH (not defined), third-stage duration (min), headache, shivering
Notes	Method of randomisation not clear and 'Risk of bias' assessment is uncertain. Written in Persian and awaiting translation

Bhatti 2014

Methods	Randomised trial.
Participants	120 women
Interventions	10 IU of oxytocin administered intramuscularly or 400 mcg of misoprostol administered sublingually
Outcomes	PPH at 500. Blood loss (mL).
Notes	Method of randomisation not clear and 'Risk of bias' assessment is uncertain. Cannot obtain full text

Boopathi 2014

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Carrillo-Gaucin 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Chalermpolprapa 2010

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Chandhiok 2006

Methods	Cluster-randomised trial.
Participants	1200 women from 30 health centres
Interventions	600 mcg of Methylergometrine administered intramuscularly or 600 mcg of misoprostol administered orally
Outcomes	PPH at 500, third-stage duration (min).,additional uterotonics,transfusion, blood loss (mL)
Notes	Method of randomisation not clear and 'Risk of bias' assessment is uncertain. Require intracluster correlation coefficient

Chatterjee 2000

Methods	Randomised trial.
Participants	200 women
Interventions	Not known dose of ergometrine administered intravenously or not known dose of misoprostol administered orally
Outcomes	Additional uterotonics, PPH (not defined), third-stage duration (min), transfusion
Notes	Method of randomisation not clear and 'Risk of bias' assessment is uncertain. Abstract only. Unable to contact authors

Chatterjee 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Chaudhuri 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Chou 2015

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Cordovani 2011

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Dabbaghi 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Dagdeviren 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Del Angel-Garcia 2006

Methods	Randomised trial.
Participants	152 women with no clear inclusion criteria
Interventions	Not known dose of carbetocin of unknown route or not known dose of oxytocin of unknown route
Outcomes	PPH (not defined).
Notes	Method of randomisation not clear and 'Risk of bias' assessment is uncertain. Abstract only. Unable to contact authors

Dell-Kuster 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Dell-Kuster 2016a

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Dell-Kuster 2017

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Deshpande 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Diop 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Dumoulin 1981

Methods	Randomised trial.
Participants	1750 women
Interventions	5 IU of oxytocin administered intramuscularly then increased to 10 IU or ergometrine 500 mcg plus 5 IU of oxytocin administered intramuscularly
Outcomes	PPH at 500, blood loss (mL).
Notes	Method of randomisation not clear and 'Risk of bias' assessment is uncertain

Dutta 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Elbohoty 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Fahmy 2015

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Fahmy 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Fakour 2013

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Frye 2015

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Fuks 2014

Methods	Open-label randomised trial.
Participants	143 women with term singleton pregnancies
Interventions	Not known dose of oxytocin of unknown route or Not known dose of oxytocin of unknown route plus 600 mcg of misoprostol administered rectally
Outcomes	Change in Hb level.
Notes	Method of randomisation not clear and 'Risk of bias' assessment is uncertain. Abstract only. Unable to contact authors

Ghulmiyyah 2017

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Gulmezoglu 2015

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Hernandez-Castro 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Islam 2008

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Jagielska 2015

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Jans 2017

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Javadi 2015

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Kabir 2015

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Khan 2013

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Koen 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Liu 2015

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Liu 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Maged 2015

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Maged 2017

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Makvandi 2013

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Mirteimouri 2013

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Mockler 2015

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Modi 2014

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Mohamadian 2013

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Mohamed 2015

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Murphy 2015

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Nankaly 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Narenji 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Neri-Mejia 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Ng 2004

Methods	Double-blinded randomised trial.
Participants	Not known how many women randomised
Interventions	Not known dose of oxytocin administered intravenously or 400 mcg of misoprostol administered orally
Outcomes	PPH at 500, PPH at 1000, additional uterotonics, transfusion, change in Hb level, blood loss (mL), fever, shivering
Notes	Method of randomisation not clear and 'Risk of bias' assessment is uncertain. Abstract only. Unable to contact authors

Nguyen-Lu 2015

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Ononge 2015

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Othman 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Pakniat 2015

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Patil 2013

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Quibel 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Rabow 2017

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Ragab 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Raghavan 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Ray 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Razali 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Reyes 2011

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Rosales-Ortiz 2014

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Sangkhomkhamhang 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Sentilhes 2015

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Senturk 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Shrestha 2008

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Shrivasatava 2012

Methods	Randomised trial.
Participants	Not known how many women randomised
Interventions	200 mcg of Methylergometrine of unknown route or 400 mcg of misoprostol administered sublingually
Outcomes	PPH (not defined), additional uterotonics, change in HB level, third-stage duration (min), blood loss (mL)
Notes	Method of randomisation not clear and 'Risk of bias' assessment is uncertain. Abstract only. Unable to contact authors

Soleimani 2014

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Sunil 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Taheripanah 2017

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Tali 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Ugwu 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Un 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Vlassoff 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Voltolini 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Weeks 2015

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Whigham 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Winikoff 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Hb, haemoglobin; **IU,** international unit;**mcg,** microgram; **mL,**: milliltre; **PPH,** postpartum haemorrhage

Characterics of ongoing studies *[ordered by study ID]*

Castro 2012

Trial name or title	Buccal misoprostol during cesarean section for preventing postpartum hemorrhage
Methods	Placebo-controlled randomised trial.
Participants	120 women undergoing an elective or emergency caesarean birth at 24 weeks of gestation or later with risk factors for PPH
Interventions	400 mcg of misoprostol administered buccally or placebo
Outcomes	PPH at 1000, additional uterotonics, transfusion.
Starting date	February 2008, Updated 2012
Contact information	Dr. Jose E. Gonzalez
Notes	This study is shown as currently recruiting participants.

Diop 2011

Trial name or title	Comparing misoprostol and oxytocin in UnijectTM for Postpartum Hemorrhage (PPH) Prevention in Mali
Methods	Double-blinded randomised trial.
Participants	140 women with a pregnancy over 34 weeks and a risk factor for PPH
Interventions	100 mcg of carbetocin administered intravenously or 10 IU of oxytocin administered intravenously
Outcomes	Change in Hb level, nausea, vomiting, fever, shivering.
Starting date	Start date not known.
Contact information	Milton Cesar Gomez Gomez
Notes	This study is shown as not yet recruiting.

Diop 2012

Trial name or title	Comparing misoprostol and oxytocin in Uniject for postpartum hemorrhage (PPH) prevention in Senegal
Methods	Open-label cluster-randomised trial.
Participants	1365 women giving birth in community health centres with a trained study provider
Interventions	600 mcg of misoprostol administered orally or 10 IU of oxytocin administered intramuscularly

Outcomes	Change in Hb level, nausea, vomiting, fever, shivering.
Starting date	June 2012
Contact information	Gynuity health projects
Notes	This study is shown as completed.

Draycott 2014

Trial name or title	Intramuscular oxytocics: a comparison study of intramuscular carbetocin, syntocinon and syntometrine for the third stage of labour following vaginal birth (IMox)
Methods	Randomised trial
Participants	Women delivering vaginally, singleton pregnancy
Interventions	One dose of 100 mcg intramuscular Carbetocin given for active management of the third stage of labour, immediately after the birth of the baby One dose of 10 IU intramuscular Syntocinon given for active management of the third stage of labour, immediately after the birth of the baby One dose of 500 mcg/5 IU intramuscular Syntometrine given for active management of the third stage of labour, immediately after the birth of the baby
Outcomes	Requirement for additional uterotonic drugs
Starting date	February 2015
Contact information	Tim Draycott, North Bristol NHS Trust/University of Bristol
Notes	Study Chair:

Gomez 2011

Trial name or title	Efficiency of carbetocin in the prevention of the postpartum haemorrhage: a clinical double-blinded randomised study
Methods	Open-label randomised trial.
Participants	Women undergoing a vaginal birth at home with a trained study provider
Interventions	600 mcg of misoprostol administered orally or 10 IU of oxytocin administered intramuscularly
Outcomes	PPH at 1000, additional uterotonics, transfusion, nausea, headache, abdominal pain
Starting date	15/07/2010

Contact information	Milton Cesar Gomez Gomez
Notes	This study is shown as not yet recruiting.

Kalahroudi 2010a

Trial name or title	Comparison of the effect of rectal misoprostol and syntometrin in prevention of postpartum hemorrhage
Methods	Double-blinded randomised trial.
Participants	200 women with a singleton pregnancy undergoing a vaginal birth
Interventions	500 mcg of ergometrine plus 5 IU of oxytocin administered intramuscularly or 600 mcg of misoprostol administered rectally
Outcomes	Additional uterotonics, change in Hb level.
Starting date	21/4/2010
Contact information	Dr. Mansoureh Samimi
Notes	This study is shown as recruitment complete.

Kalahroudi 2010b

Trial name or title	Comparison effect of carbetocine and syntometrin in prevention of postpartum hemorrhage
Methods	Double-blinded randomised trial.
Participants	200 women with a singleton pregnancy undergoing a vaginal birth
Interventions	500 mcg of ergometrine plus 5 IU of oxytocin administered intramuscularly or 100 mcg of carbetocin administered intramuscularly
Outcomes	Additional uterotonics, change in Hb level.
Starting date	21/1/2010
Contact information	Dr. Mansoureh Samimi
Notes	This study is shown as recruitment complete.

Moradi 2010

Trial name or title	Comparison of misoprostol and oxytocin in reduction of postpartum hemorrhage
Methods	Randomised trial.
Participants	300 women with singleton, term pregnancies.
Interventions	10 IU of oxytocin administered intravenously or 400 mcg of misoprostol administered orally
Outcomes	Change in haemoglobin.
Starting date	22/12/2009
Contact information	Simindokht Moradi
Notes	This study is shown as recruitment complete.

Shahboodaghi 2013

Trial name or title	Misoprostol versus oxytocin for prevention of post partum hemorrhage
Methods	Double-dummy randomised trial.
Participants	400 women undergoing vaginal birth with a singleton pregnancy
Interventions	400 mcg misoprostol administered orally or 20 IU of oxytocin administered through an intravenous infusion
Outcomes	Change in Hb level, vomiting, fever, shivering.
Starting date	May 2013
Contact information	Dr Minoo Rajaei
Notes	This study is shown as ongoing, but not recruiting participants

Sweed 2014

Trial name or title	Comparison between rectal & sublingual misoprostol before caesarian section to reduce intra & post-operative blood loss
Methods	Placebo-controlled randomised trial.
Participants	635 women undergoing elective caesarean with a singleton term pregnancy and only 1 previous caesarean
Interventions	400 mcg of misoprostol administered rectally or 400 mcg of misoprostol administered sublingually or placebo
Outcomes	Change in Hb level, blood loss.

Starting date	February 2013
Contact information	Mohamed S Sweed,
Notes	This study is shown as completed.

Widmer 2016

Trial name or title	Room temperature stable carbetocin for the prevention of postpartum haemorrhage during the third stage of labour in women delivering vaginally
Methods	Randomized, non-inferiority trial at 22 centres in 10 countries
Participants	Women delivering vaginally, cervical dilatation equal to or less than 6cm, singleton pregnancy
Interventions	Carbetocin RTS 100 micrograms solution for intramuscular (IM) injection to be administered once during the third stage of labour Oxytocin 10 IU solution for intramuscular (IM) injection to be administered once during the third stage of labour
Outcomes	The proportion of women with blood loss of 500 mL or more or the use of additional uterotonics at one hour and up to two hours for women who continue to bleed after one hour (composite primary outcome). The blood loss will be measured with a plastic drape placed under the woman's buttocks
Starting date	July 2015
Contact information	Mariana Widmer (widmerm@who.int)
Notes	ACTRN12614000870651

Hb, haemoglobin; **IU,** international unit;**mcg,** microgram; **PPH,** postpartum haemorrhage; **RTS,** room temperature stable

Appendix 1. Search terms

ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP)
Third stage AND labo(u)r AND oxytocin
Third stage AND labo(u)r AND misoprostol
Third stage AND labo(u)r AND carbetocin
Third stage AND labo(u)r AND ergometrine
uterotonic* AND oxytocin
uterotonic* AND misoprostol
uterotonic* AND carbetocin
uterotonic* AND ergometrine
uterotonic* AND labo(u)r
uterotonic* AND h(a)emorrhage
h(a)emorrhage AND postpartum AND ergometrine
h(a)emorrhage AND postpartum AND oxytocin
h(a)emorrhage AND postpartum AND carbetocin
h(a)emorrhage AND postpartum AND misoprostol

Appendix 2. Network diagrams for secondary outcomes and subgroup analyses

Please see NIHR HTA report for all diagrams (link).

Appendix 3. Subgroup and sensitivity analyses for PPH ≥ 1000 mL

Please see NIHR HTA report for all diagrams (https://www.journalslibrary.nihr.ac.uk/programmes/hta/1413917/#/)

CONTRIBUTIONS OF AUTHORS

Ioannis D Gallos (IDG) and Arri Coomarasamy (AC) conceived the idea for this study. IDG, Helen M Williams (HMW), Malcolm J Price (MP), Abi Merriel (AM), Harold Gee (HG), David Lissauer (DL), Vidhya Moorthy (VM), Özge Tunçalp (OT), A Metin Gülmezoglu (AMG), Jonathan J Deeks (JJD), G Justus Hofmeyr (GJH) and AC designed the meta-analysis. IDG designed all electronic data collection forms. IDG, HMW, AM, HG, DL, VM and OT screened trials and extracted data. MP and Aurelio Tobias (AT) performed the statistical analysis. MP, AT and JJD provided statistical advice and input. IDG drafted the protocol and all versions of the review. HMW, MP, AM, HG, DL, OT, MW, AMG, AT, JJD, GJH and AC edited and revised the review.

DECLARATIONS OF INTEREST

Ioannis D Gallos (IDG): is a co-applicant to the UK National Institute for Health Research HTA Project Award 14/139/17 entitled "Uterotonic drugs for preventing postpartum haemorrhage: a network meta-analysis and cost-effectiveness analysis". He has been involved in one or more previous or ongoing trials related to the use of uterotonics for the prevention of PPH that could be eligible for inclusion in this review. He will not participate in any decisions regarding these trials (i.e. assessment for inclusion/exclusion, trial quality, data extraction) for the purposes of this review or future updates - these tasks will be carried out by other members of the team who are not directly involved in the trials. Ferring Pharmaceuticals and Novartis have supplied carbetocin and oxytocin for studies and an ongoing study is supported by WHO/Merck for Mothers. IDG has been supported by the MSD for mothers initiative for travel to a meeting for the study.

Helen M Williams (HMW): is part-funded by the Birmingham Women's NHS Foundation Trust, and a co-applicant to the UK National Institute for Health Research HTA Project Award 14/139/17 entitled "Uterotonic drugs for preventing postpartum haemorrhage: a network meta-analysis and cost-effectiveness analysis". Her salary is part-funded by Tommy's. She is a member of the Executive Board of

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Internal sources

- University of Birmingham, UK.

The authors of this review are employed by the institutions indicated by their respective affiliations except where otherwise stated.

- World Health Organization, Switzerland.

The authors of this review are employed by the institutions indicated by their respective affiliations except where otherwise stated.

- Sandwell and West Birmingham NHS Trust, UK.

The authors of this review are employed by the institutions indicated by their respective affiliations except where otherwise stated.

- University of the Witwatersrand, South Africa.

The authors of this review are employed by the institutions indicated by their respective affiliations except where otherwise stated.

External sources

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are some differences between the published protocol for this review (Gallos 2015) and the full review, these are listed below.

Objectives

We have clarified the objectives of this review.

In our protocol the stated objectives were: We aim to assess the clinical effectiveness and side-effect profile of uterotonic drugs to prevent PPH, and to generate a clinically useful ranking of available uterotonics according to their effectiveness and side-effects. We will explore the effects according to various key prognostic and treatment factors. The population of interest is women following a vaginal birth or a caesarean section in the hospital or the community setting. All uterotonic drugs considered by the WHO are eligible and the outcomes include blood loss-related outcomes and side-effects.

In the review, our objectives are listed as:

Primary

To identify the most effective uterotonic drug(s) to prevent postpartum haemorrhage (PPH) with a favourable side-effect profile, and to generate a clinically useful ranking of all available uterotonics.

Secondary

To provide the relative effectiveness and side-effect profile of each drug for our primary outcomes within: a) Population subgroups (prior risk of PPH, mode of birth and healthcare setting) and b) Treatment subgroups (different dosages, routes or regimens of administration of each uterotonic drug).

Methods/types of agents

The text in this section has been edited to add sensitivity analyses that became necessary during the review and explain how we grouped the agents for analysis.

In the protocol, this section stated:

We will consider trials of uterotonics described by WHO (WHO 2012) (oxytocin, ergometrine, misoprostol, carbetocin, or combinations of uterotonics) administered prophylactically by healthcare professionals for preventing PPH via any systemic route (sublingual, subcutaneous, intramuscular, rectal, oral, intravenous bolus and/or infusion) compared with another uterotonic or with placebo or no treatment. If we identify in the included studies interventions that we are not aware of, we will consider them as eligible and include them in the network after assessing their comparability with those named above. We will include trials in which non-pharmacologic co-interventions such as controlled cord traction, cord clamping, or uterine massage was performed as a randomised intervention in all arms of the trial. We will stratify all drugs according to mode of birth, prior risk of PPH, healthcare setting, specific dosage, regimen and route, to detect inequalities in subgroups that could affect comparative effectiveness.

Figure 1 (in the published protocol) shows the overall network of eligible comparisons in the review at a drug level.

Multi-arm trials that compare different dosages, regimens or routes of one uterotonic drug, but also compare those versus another uterotonic drug, will be included. Intervention arms of different dosages, regimens or routes of the same uterotonic drug will be merged together for the global analysis of all outcomes and treated as separate independent comparisons only for the relevant subgroup analysis according to dosage, regimen and route of drug administration, while taking into account the correlation between the comparisons. We will exclude trials comparing exclusively different dosages, regimens or routes of administration of the same uterotonic drug. The review will be restricted to studies evaluating uterotonic drugs administered systemically at the birth of the baby for preventing PPH. Studies considering non-uterotonic drugs, uterotonic drugs administered locally (for example, via intraumbilical or intrauterine routes) or at a later stage of delivery (for example, for the treatment of PPH or for retained placenta) will be excluded.

In our review this section now states:

Trials were eligible if they administered uterotonic agents of any dosage, route or regimen systemically following birth for preventing PPH, and compared them against other uterotonic agents, placebo or no treatment. Trials evaluating uterotonic drugs administered locally or not immediately after birth, or exclusively comparing different dosages, routes or regimens of the same uterotonic agent were excluded. We included trials in which non-pharmacologic co-interventions such as controlled cord traction, cord clamping, or uterine massage was performed as a randomised intervention in all arms of the trial and the effects of such co-interventions were tested through a sensitivity analysis.

We classified drugs into oxytocin, carbetocin, misoprostol, ergometrine (included also ergonovine, methylergonovine), oxytocin plus ergometrine (Syntometrine, oxytocin combined with ergometrine, ergonovine, or methylergonovine), and oxytocin plus misoprostol. We excluded synthetic prostaglandin analogues of PGF2α (carboprost), and PGE2 (prostin, sulprostone), because these drugs are usually used for *treating* (and not *preventing*) PPH, and are not currently recommended by the World Health Organization (WHO) as alternatives (WHO 2012).

Methods/search methods

The search methods have been updated in line with the current standard search methods text of Cochrane Pregnancy and Childbirth.

Methods/types of outcomes/secondary outcomes

We have edited the outcome 'clinical signs of blood loss' to 'clinical signs of excessive blood loss (as defined by the trialists).'

Methods/investigation of heterogeneity and inconsistency and also subgroup analysis

We have edited the intervention subgroups for exploring heterogeneity and inconsistency and also subgroup analysis. In the protocol, these sections stated:

Intervention: dose, regimen or route.

In our review these sections now state:

Intervention: Dose of misoprostol (≥ 600 mcg versus < 600 mcg), and regimen of oxytocin (bolus versus bolus plus infusion versus infusion only).

Methods/investigation of heterogeneity and inconsistency and also subgroup analysis

We have carried out additional sensitivity analyses that became necessary during the conduct of the review. These are listed below:

1. Trials that also randomised participants to co-interventions such as uterine massage or controlled cord traction.
2. Trials with more than 10% missing data.
3. Trials published before 1990.

Analysis

Since publication of the protocol for this review, further methods became available to perform the analysis with a frequentist approach in STATA. We changed our analysis for this reason to STATA rather than WinBUGS and a Bayesian environment.

'Summary of findings' table

We have added a GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis, which was not planned during the protocol stage as the methods for this only became available recently for network meta-analyses.