Uterotonic agents for first-line treatment of postpartum haemorrhage

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TABLE OF CONTENTS

[Intervention Review]

Uterotonic agents for first-line treatment of postpartum haemorrhage: a network meta-analysis

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ABSTRACT

Background

Postpartum haemorrhage (PPH), defined as a blood loss of 500 mL or more after birth, is the leading cause of maternal death worldwide. The World Health Organization (WHO) recommends that all women giving birth should receive a prophylactic uterotonic agent. Despite the routine administration of a uterotonic agent for prevention, PPH remains a common complication causing one-quarter of all maternal deaths globally. When prevention fails and PPH occurs, further administration of uterotonic agents as 'first-line' treatment is recommended. However, there is uncertainty about which uterotonic agent is best for the 'first-line' treatment of PPH.

Objectives

To identify the most effective uterotonic agent(s) with the least side-effects for PPH treatment, and generate a meaningful ranking among all available agents according to their relative effectiveness and side-effect profile.

Search methods

We searched the Cochrane Pregnancy and Childbirth's Trials Register, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) (5 May 2020), and the reference lists of all retrieved studies.

Selection criteria

All randomised controlled trials or cluster-randomised trials comparing the effectiveness and safety of uterotonic agents with other uterotonic agents for the treatment of PPH were eligible for inclusion.

Data collection and analysis

Two review authors independently assessed all trials for inclusion, extracted data and assessed each trial for risk of bias. Our primary outcomes were additional blood loss of 500 mL or more after recruitment to the trial until cessation of active bleeding and the composite

outcome of maternal death or severe morbidity. Secondary outcomes included blood loss-related outcomes, morbidity outcomes, and patient-reported outcomes. We performed pairwise meta-analyses and indirect comparisons, where possible, but due to the limited number of included studies, we were unable to conduct the planned network meta-analysis. We used the GRADE approach to assess the certainty of evidence.

Main results

Seven trials, involving 3738 women in 10 countries, were included in this review. All trials were conducted in hospital settings. Randomised women gave birth vaginally, except in one small trial, where women gave birth either vaginally or by caesarean section. Across the seven trials (14 trial arms) the following agents were used: six trial arms used oxytocin alone; four trial arms used misoprostol plus oxytocin; three trial arms used misoprostol; one trial arm used Syntometrine® (oxytocin and ergometrine fixed-dose combination) plus oxytocin infusion.

Pairwise meta-analysis of two trials (1787 participants), suggests that misoprostol, as first-line treatment uterotonic agent, probably increases the risk of blood transfusion (risk ratio (RR) 1.47, 95% confidence interval (CI) 1.02 to 2.14, moderate-certainty) compared with oxytocin. Low-certainty evidence suggests that misoprostol administration may increase the incidence of additional blood loss of 1000 mL or more (RR 2.57, 95% CI 1.00 to 6.64). The data comparing misoprostol with oxytocin is imprecise, with a wide range of treatment effects for the additional blood loss of 500 mL or more (RR 1.66, 95% CI 0.69 to 4.02, low-certainty), maternal death or severe morbidity (RR 1.98, 95% CI 0.36 to 10.72, low-certainty, based on one study n = 809 participants, as the second study had zero events), and the use of additional uterotonics (RR 1.30, 95% CI 0.57 to 2.94, low-certainty). The risk of side-effects may be increased with the use of misoprostol compared with oxytocin: vomiting (2 trials, 1787 participants, RR 2.47, 95% CI 1.37 to 4.47, high-certainty) and fever (2 trials, 1787 participants, RR 3.43, 95% CI 0.65 to 18.18, low-certainty).

According to pairwise meta-analysis of four trials (1881 participants) generating high-certainty evidence, misoprostol plus oxytocin makes little or no difference to the use of additional uterotonics (RR 0.99, 95% CI 0.94 to 1.05) and to blood transfusion (RR 0.95, 95% CI 0.77 to 1.17) compared with oxytocin. We cannot rule out an important benefit of using the misoprostol plus oxytocin combination over oxytocin alone, for additional blood loss of 500 mL or more (RR 0.84, 95% CI 0.66 to 1.06, moderate-certainty). We also cannot rule out important benefits or harms for additional blood loss of 1000 mL or more (RR 0.76, 95% CI 0.43 to 1.34, moderate-certainty, 3 trials, 1814 participants, one study reported zero events), and maternal mortality or severe morbidity (RR 1.09, 95% CI 0.35 to 3.39, moderate-certainty). Misoprostol plus oxytocin increases the incidence of fever (4 trials, 1866 participants, RR 3.07, 95% CI 2.62 to 3.61, high-certainty), and vomiting (2 trials, 1482 participants, RR 1.85, 95% CI 1.16 to 2.95, high-certainty) compared with oxytocin alone.

For all outcomes of interest, the available evidence on the misoprostol versus Syntometrine® plus oxytocin combination was of very low-certainty and these effects remain unclear.

Although network meta-analysis was not performed, we were able to compare the misoprostol plus oxytocin combination with misoprostol alone through the common comparator of oxytocin. This indirect comparison suggests that the misoprostol plus oxytocin combination probably reduces the risk of blood transfusion (RR 0.65, 95% CI 0.42 to 0.99, moderate-certainty) and may reduce the risk of additional blood loss of 1000 mL or more (RR 0.30, 95% CI 0.10 to 0.89, low-certainty) compared with misoprostol alone. The combination makes little or no difference to vomiting (RR 0.75, 95% CI 0.35 to 1.59, high-certainty) compared with misoprostol alone. Misoprostol plus oxytocin compared to misoprostol alone are compatible with a wide range of treatment effects for additional blood loss of 500 mL or more (RR 0.51, 95% CI 0.20 to 1.26, low-certainty), maternal mortality or severe morbidity (RR 0.55, 95% CI 0.07 to 4.24, low-certainty), use of additional uterotonics (RR 0.76, 95% CI 0.33 to 1.73, low-certainty), and fever (RR 0.90, 95% CI 0.17 to 4.77, low-certainty).

Authors' conclusions

The available evidence suggests that oxytocin used as first-line treatment of PPH probably is more effective than misoprostol with less side-effects. Adding misoprostol to the conventional treatment of oxytocin probably makes little or no difference to effectiveness outcomes, and is also associated with more side-effects. The evidence for most uterotonic agents used as first-line treatment of PPH is limited, with no evidence found for commonly used agents, such as injectable prostaglandins, ergometrine, and Syntometrine®.

PLAIN LANGUAGE SUMMARY

Which drug is best for treating excessive bleeding after childbirth?

What is the issue?

The most common reason why mothers die during childbirth is excessive bleeding, which is known as postpartum haemorrhage, when blood loss equals or exceeds 500 mL. This emergency condition is usually caused by failure of the uterus to contract and close the vessels that carried blood to the placenta. The World Health Organization (WHO) recommends giving drugs that make the uterus contract more effectively (uterotonic drugs) and reduce the risk for excessive bleeding. Although these drugs are given to the mother immediately after the birth of her baby, some women will still experience heavy bleeding and will require further treatment.

Why is this important?

The administration of uterotonic drugs is the main treatment when prevention fails, and excessive bleeding occurs. Available uterotonic treatments include oxytocin, carbetocin, ergometrine, misoprostol, injectable prostaglandins, and combinations of these drugs, which

differ in terms of effectiveness and side-effects. The aim of this Cochrane Review is to identify the best drug with the least side-effects for treating excessive bleeding after childbirth.

What evidence did we find?
We searched for evidence in May 2020 and found seven studies involving 3738 women. Women gave birth mostly vaginally in hospital settings and had received uterotonic drugs to prevent postpartum haemorrhage. The drugs used for treating heavy bleeding in these studies were misoprostol (tablets dissolved under the tongue, pills or rectal suppositories), oxytocin (given into a vein or muscle), a combination of misoprostol with oxytocin and a combination of Syntometrine® (ergometrine plus oxytocin combination injected into muscle) with oxytocin.

Two studies, involving 1787 women, compared misoprostol with oxytocin for the initial treatment of excessive bleeding after birth. We found that misoprostol probably increases the risk of requiring a blood transfusion compared with oxytocin and may also increase the risk of suffering an additional blood loss of 1000 mL or more after initiation of treatment and until the bleeding stops. From the available data, we cannot learn much for the outcomes of suffering an additional blood loss of 500 mL or more, maternal death or severe illness related to excessive blood loss, and the need for additional uterotonic drugs to stop the bleeding. In terms of side-effects, misoprostol increases the risk for vomiting and may also increase the incidence of fever compared with oxytocin.

Four studies, involving 1881 women, compared misoprostol given in combination with oxytocin against oxytocin given alone. The drug combination makes little or no difference to the use of additional uterotonics, and blood transfusion compared with oxytocin given alone. However, we were not able to identify which of these drugs works best for reducing additional blood loss of 500 mL or more, additional blood loss of 1000 mL or more, and maternal death or severe illness related to excessive blood loss. In terms of side-effects, the drug combination increases the occurrence of both fever and vomiting.

One trial with only 64 women compared misoprostol with Syntometrine® combined with oxytocin. The available evidence was of very low certainty and thus we were unable to identify the best performing drug among them.

We also compared the combination of misoprostol and oxytocin against misoprostol alone. These drugs have not been compared directly in studies. However, both drugs have been compared against oxytocin, and thus we were able to compare them indirectly. The drug combination probably reduces the risk of blood transfusion and may reduce the risk of additional blood loss of 1000 mL or more, but makes little or no difference to vomiting compared with misoprostol alone. However, we cannot learn much for the outcomes of additional blood loss of 500 mL or more, maternal death or severe illness related to excessive blood loss, use of additional uterotonic drugs, and fever.

What does this mean?
We found that oxytocin is probably more effective than misoprostol and is also associated with less side-effects. Giving misoprostol together with oxytocin probably does not improve effectiveness and increases side-effects. The evidence for most available drugs used as first-line treatment of postpartum haemorrhage is limited, with no evidence found for several drugs currently in use.

SUMMARY OF FINDINGS

Summary of findings 1. Additional blood loss of 500 mL or more

Patient or population: women in the third stage of labour with PPH
Interventions: multiple uterotonic agents (misoprostol, misoprostol plus oxytocin)
Comparison/Standard care (reference): multiple uterotonic agents (oxytocin, Syntometrine® plus oxytocin)
Outcome: additional blood loss of 500 mL or more after recruitment to cessation of active bleeding
Setting: hospital

Uterotonic agent(s)	Anticipated absolute effects* (95% CI)			Direct evidence		
	Risk with standard care	Risk with intervention	Risk difference with intervention	RR (95% CI)	Nº of participants (studies)	Certainty
Misoprostol versus oxytocin	82 per 1000 (oxytocin)	136 per 1000 (misoprostol)	54 more per 1000 (from 25 fewer to 247 more) with misoprostol compared with oxytocin	1.66 (0.69 to 4.02)	1787 women (2 RCTs)	⊕⊕⊖⊖ LOW[a]
Misoprostol plus oxytocin versus oxytocin	211 per 1000 (oxytocin)	177 per 1000 (misoprostol plus oxytocin)	34 fewer per 1000 (from 72 fewer to 13 more) with misoprostol plus oxytocin compared with oxytocin alone	0.84 (0.66 to 1.06)	1873 women (4 RCTs)	⊕⊕⊕⊖ MODERATE[b]
Misoprostol versus Syntometrine®plus oxytocin	Not estimable	Not estimable	Not estimable	Not estimable	Not reported by included studies	-

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; The true effect is likely to be substantially different from the estimate of effect.

[a] Direct evidence downgraded -2 due to severe unexplained statistical heterogeneity and serious imprecision.
[b] Direct evidence downgraded -1 due to serious imprecision.

Summary of findings 2. Composite of death or severe morbidity

Patient or population: women in the third stage of labour with PPH
Interventions: multiple uterotonic agents (misoprostol, misoprostol plus oxytocin)
Comparison/Standard care (reference): multiple uterotonic agents (oxytocin, Syntometrine® plus oxytocin)
Outcome: composite of death, hysterectomy, transfer to higher care, organ dysfunction, coagulopathy, shock
Setting: hospital

Uterotonic agent(s)	Anticipated absolute effects* (95% CI)			Direct evidence		
	Risk with standard care	Risk with intervention	Risk difference with intervention	RR (95% CI)	Nº of participants (studies)	Certainty
Misoprostol versus oxytocin	2 per 1000 (oxytocin)	4 per 1000 (misoprostol)	2 more per 1000 (from 1 fewer to 22 more) with misoprostol compared with oxytocin	1.98 (0.36 to 10.72)	809 women (1 RCT)	⊕⊕⊖⊖ LOW[a]
Misoprostol plus oxytocin versus oxytocin	14 per 1000 (oxytocin)	15 per 1000 (misoprostol plus oxytocin)	1 more per 1000 (from 9 fewer to 33 more) with misoprostol plus oxytocin compared with oxytocin alone	1.09 (0.35 to 3.39)	1881 women (4 RCTs)	⊕⊕⊕⊖ MODERATE[b]
Misoprostol versus Syntometrine® plus oxytocin	31 per 1000 (Syntometrine® plus oxytocin)	10 per 1000 (misoprostol)	21 fewer per 1000 (from 31 fewer to 215 more) with misoprostol compared with Syntometrine® plus oxytocin	0.33 (0.01 to 7.89)	64 women (1 RCT)	⊕⊖⊖⊖ VERY LOW[c]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Direct evidence downgraded -2 due to very serious imprecision.
[b] Direct evidence downgraded -1 due to serious imprecision.
[c] Direct evidence downgraded -3 due to multiple limitations in study design and very serious imprecision.

Summary of findings 3. Use of additional uterotonics

Patient or population: women in the third stage of labour with PPH
Interventions: multiple uterotonic agents (misoprostol, misoprostol plus oxytocin)
Comparison/Standard care (reference): multiple uterotonic agents (oxytocin, Syntometrine® plus oxytocin)
Outcome: use of additional uterotonics
Setting: hospital

Uterotonic agent(s)	Anticipated absolute effects* (95% CI)			Direct evidence		
	Risk with standard care	Risk with intervention	Risk difference with intervention	RR (95% CI)	Nº of participants (studies)	Certainty
Misoprostol versus oxytocin	86 per 1000 (oxytocin)	112 per 1000 (misoprostol)	26 more per 1000 (from 37 fewer to 167 more) with misoprostol compared with oxytocin	1.30 (0.57 to 2.94)	1787 women (2 RCTs)	⊕⊕⊖⊖ LOW[a]
Misoprostol plus oxytocin versus oxytocin	322 per 1000 (oxytocin)	319 per 1000 (misoprostol plus oxytocin)	3 fewer per 1000 (from 19 fewer to 16 more) with misoprostol plus oxytocin compared with oxytocin alone	0.99 (0.94 to 1.05)	1866 women (4 RCTs)	⊕⊕⊕⊕ HIGH
Misoprostol versus Syntometrine® plus oxytocin	344 per 1000 (Syntometrine® plus oxytocin)	62 per 1000 (misoprostol)	282 fewer per 1000 (from 330 fewer to 82 fewer) with misoprostol compared with Syntometrine® plus oxytocin	0.18 (0.04 to 0.76)	64 women (1 RCT)	⊕⊖⊖⊖ VERY LOW[b]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Direct evidence downgraded -2 due to severe unexplained statistical heterogeneity and serious imprecision.
[b] Direct evidence downgraded -3 due to multiple limitations in study design and serious imprecision.

Summary of findings 4. Additional blood loss of 1000 mL or more

Patient or population: women in the third stage of labour with PPH
Interventions: multiple uterotonic agents (misoprostol, misoprostol plus oxytocin)
Comparison/Standard care (reference): multiple uterotonic agents (oxytocin, Syntometrine® plus oxytocin)
Outcome: additional blood loss of 1000 mL or more after recruitment to cessation of active bleeding
Setting: hospital

Uterotonic agent(s)	Anticipated absolute effects* (95% CI)			Direct evidence		
	Risk with standard care	Risk with intervention	Risk difference with intervention	RR (95% CI)	Nº of participants (studies)	Certainty
Misoprostol versus oxytocin	7 per 1000 (oxytocin)	18 per 1000 (misoprostol)	11 more per 1000 (from 0 fewer to 38 more) with misoprostol compared with oxytocin	2.57 (1.00 to 6.64)	1787 women (2 RCTs)	⊕⊕⊖⊖ LOW[a]
Misoprostol plus oxytocin versus oxytocin	29 per 1000 (oxytocin)	22 per 1000 (misoprostol plus oxytocin)	7 fewer per 1000 (from 16 fewer to 10 more) with misoprostol plus oxytocin compared with oxytocin alone	0.76 (0.43 to 1.34)	1814 women (3 RCTs)	⊕⊕⊕⊖ MODERATE[b]
Misoprostol versus Syntometrine®plus oxytocin	Not estimable	Not estimable	Not estimable	Not estimable	Not reported by included studies	-

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Direct evidence downgraded -2 due to very serious imprecision.
[b] Direct evidence downgraded -1 due to serious imprecision.

Summary of findings 5. Blood transfusion or other blood products

Patient or population: women in the third stage of labour with PPH
Interventions: multiple uterotonic agents (misoprostol, misoprostol plus oxytocin)

Comparison/Standard care (reference): multiple uterotonic agents (oxytocin, Syntometrine® plus oxytocin)
Outcome: blood transfusion or other blood products
Setting: hospital

Uterotonic agent(s)	Anticipated absolute effects* (95% CI)			Direct evidence		
	Risk with standard care	Risk with intervention	Risk difference with intervention	RR (95% CI)	Nº of participants (studies)	Certainty
Misoprostol versus oxytocin	49 per 1000 (oxytocin)	72 per 1000 (misoprostol)	23 more per 1000 (from 1 more to 56 more) with misoprostol compared with oxytocin	1.47 (1.02 to 2.14)	1787 women (2 RCTs)	⊕⊕⊕⊖ MODERATE[a]
Misoprostol plus oxytocin versus oxytocin	158 per 1000 (oxytocin)	150 per 1000 (misoprostol plus oxytocin)	8 fewer per 1000 (from 36 fewer to 27 more) with misoprostol plus oxytocin compared with oxytocin alone	0.95 (0.77 to 1.17)	1877 women (4 RCTs)	⊕⊕⊕⊕ HIGH
Misoprostol versus Syntometrine®plus oxytocin	Not estimable	Not estimable	Not estimable	Not estimable	Not reported by included studies	-

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Direct evidence downgraded -1 due to indirectness.

Summary of findings 6. Side effects: fever

Patient or population: women in the third stage of labour with PPH
Interventions: multiple uterotonic agents (misoprostol, misoprostol plus oxytocin)
Comparison/Standard care (reference): multiple uterotonic agents (oxytocin, Syntometrine® plus oxytocin)
Outcome: fever
Setting: hospital

Uterotonic agent(s)	Anticipated absolute effects* (95% CI)			Direct evidence		
	Risk with standard care	Risk with intervention	Risk difference with intervention	RR (95% CI)	Nº of participants (studies)	Certainty
Misoprostol versus oxytocin	96 per 1000 (oxytocin)	331 per 1000 (misoprostol)	234 more per 1000 (from 34 fewer to 1000 more) with misoprostol compared with oxytocin	3.43 (0.65 to 18.18)	1787 women (2 RCTs)	⊕⊕⊙⊙ LOW[a]
Misoprostol plus oxytocin versus oxytocin	151 per 1000 (oxytocin)	463 per 1000 (misoprostol plus oxytocin)	312 more per 1000 (from 244 more to 393 more) with misoprostol plus oxytocin compared with oxytocin alone	3.07 (2.62 to 3.61)	1866 women (4 RCTs)	⊕⊕⊕⊕ HIGH
Misoprostol versus Syntometrine® plus oxytocin	Not estimable	Not estimable	Not estimable	Not estimable	Not reported by included studies	-

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Direct evidence downgraded -2 due to severe unexplained statistical heterogeneity and serious imprecision.

Summary of findings 7. Side effects: vomiting

Patient or population: women in the third stage of labour with PPH
Interventions: multiple uterotonic agents (misoprostol, misoprostol plus oxytocin)
Comparison/Standard care (reference): multiple uterotonic agents (oxytocin, Syntometrine® plus oxytocin)
Outcome: vomiting
Setting: hospital

Uterotonic agent(s)	Anticipated absolute effects* (95% CI)			Direct evidence		
	Risk with standard care	Risk with intervention	Risk difference with intervention	RR (95% CI)	Nº of participants	Certainty

					(studies)	
Misoprostol versus oxytocin	19 per 1000 (oxytocin)	47 per 1000 (misoprostol)	28 more per 1000 (from 7 more to 66 more) with misoprostol compared with oxytocin	2.47 (1.37 to 4.47)	1787 women (2 RCTs)	⊕⊕⊕⊕ HIGH
Misoprostol plus oxytocin versus oxytocin	35 per 1000 (oxytocin)	64 per 1000 (misoprostol plus oxytocin)	29 more per 1000 (from 6 more to 68 more) with misoprostol plus oxytocin compared with oxytocin alone	1.85 (1.16 to 2.95)	1482 women (2 RCTs)	⊕⊕⊕⊕ HIGH
Misoprostol versus Syntometrine®plus oxytocin	Not estimable	Not estimable	Not estimable	Not estimable	Not reported by included studies	-

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

BACKGROUND

Postpartum haemorrhage (PPH), defined as a blood loss of 500 mL or more after birth, is the leading cause of maternal death worldwide, accounting for up to 27% of maternal deaths (Say 2014). Almost all maternal deaths (99%) due to PPH occur in low- and lower-middle income countries (Say 2014). When a mother dies from PPH, she often leaves behind a young family and her infant has less than a 20% chance of surviving past the first month (Say 2014). Even when death is avoided, it can result in major maternal morbidity, such as the need for surgery or hysterectomy and blood transfusions (Carroll 2016).

The most common cause of PPH is uterine atony (failure of the uterus to contract after birth). Therefore, the World Health Organization (WHO) recommends prophylactic administration of agents that increase uterine contractility (uterotonics) for all births (WHO 2018). Despite the administration of effective uterotonic agents for PPH prevention, PPH is still a very common complication, occurring in up to 15% of women giving birth (Gallos 2018). When prevention fails and PPH occurs, further administration of uterotonic agents as 'first-line' treatment is recommended (WHO 2012). There are several uterotonics available for treating PPH, including oxytocin, ergometrine, misoprostol, carbetocin, injectable prostaglandins, and combination agents. Each of these agents differs in terms of effectiveness and side-effects, which makes it difficult deciding which uterotonic agent is best for the 'first-line' treatment of PPH.

Why it is important to do this review

A Cochrane Review evaluated the interventions used for treating PPH, including pairwise meta-analyses of randomised trials comparing different uterotonic agents (Mousa 2014). However, conventional pairwise meta-analyses can only generate effect estimates for those treatment interventions that have been compared in head-to-head trials. Therefore, in the absence of a single high-quality, randomised controlled trial comparing all uterotonic agents, uncertainty remains about which is the best for PPH treatment.

Where several competing treatment options exist, not all of which have been directly compared, a network meta-analysis may be better able to allow for more comparisons to be made and a more comprehensive synthesis of relative effects for all available uterotonic agents. A network meta-analysis, unlike conventional Cochrane Reviews, simultaneously pools all direct and indirect evidence into one single coherent analysis (Caldwell 2005; Caldwell 2010). Indirect evidence is obtained by inferring the relative effectiveness of two competing treatments through a common comparator, even when these two drugs have not been compared directly (Caldwell 2010). A network meta-analysis also calculates the probability for each competing agent to constitute the most effective agent with the least side-effects, thereby allowing ranking of the available agents.

OBJECTIVES

To identify the most effective uterotonic agent(s) with the least side-effects through network meta-analysis for postpartum haemorrhage treatment, and generate a ranking among all available agents according to their relative effectiveness and side-effects profile.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials or cluster-randomised trials comparing the effectiveness and side-effects of uterotonic agents with other uterotonic agents for treating postpartum haemorrhage (PPH) were eligible for inclusion. Cross-over trials and quasi-randomised trials were excluded. The cross-over study design is inappropriate to investigate the effectiveness of PPH treatment, and quasi-randomisation rather than true randomisation brings an elevated risk of bias that we wish to eliminate for the purpose of this review. Randomised trials published only as abstracts were eligible only if sufficient information could be retrieved.

Types of participants

This review included trials involving women with PPH after a vaginal or caesarean birth in hospital or community settings.

Types of interventions

Trials were eligible for inclusion if they studied the systemic administration of uterotonic agents of any dosage, route or regimen for the treatment of primary PPH and compared them with any other uterotonic agent.

We classified the uterotonic agents into two distinct categories and both were of direct interest to this review. The first category included single agents such as oxytocin, ergometrine (including also ergonovine, and methylergonovine), misoprostol, carbetocin, and injectable prostaglandins (i.e. carboprost tromethamine or sulprostone). The second category included combination agents such as ergometrine plus oxytocin (either Syntometrine® as a fixed-dose combination drug containing 5 international units (IU) of oxytocin and 500 mcg of ergometrine, or any oxytocin dose and route when combined with any dose and route of ergometrine, ergonovine, or methylergonovine), and misoprostol plus oxytocin (any dose and route of oxytocin when combined with any dose and route of misoprostol).

We excluded all trials evaluating uterotonic agents not administered systemically (e.g. intrauterine administration) as well as those comparing exclusively different dosages, routes or regimens of the same uterotonic agent. Trials comparing other interventions including non-uterotonic drugs, such as tranexamic acid, or surgical procedures were also excluded. If we had identified interventions that we were not aware of, we would have considered them as eligible and included them in the analysis as a supplementary set of interventions after assessing their comparability with the interventions of direct interest. We merged different doses and routes of the same drug and planned to explore dose- and route-related effects in subgroup analyses, if sufficient studies were available.

For the purpose of this review, we assumed that any woman meeting our inclusion criteria is, in principle, equally likely to be randomised to any of the available uterotonic agents.

Types of outcome measures

We estimated the relative effects of the competing uterotonic agents according to the following primary and secondary outcomes.

Primary outcomes

- Additional blood loss of 500 mL or more after recruitment to the trial until cessation of active bleeding
- Composite outcome of maternal death or severe morbidity (e.g. hysterectomy, any organ dysfunction, transfer to higher level of care, coagulopathy, shock as defined by trialists)

Secondary outcomes

- Maternal death
- Need for additional uterotonics
- Additional blood loss of 1000 mL or more after recruitment to the trial until cessation of active bleeding
- Additional surgical procedures (e.g. hysterectomy, balloon insertion, pack insertion, arterial ligation, embolisation and compression sutures)
- Blood transfusion or transfusion of other blood products
- Mean additional blood loss (mL)
- Change in haemoglobin measurements before and after birth (g/L)
- Side-effects: fever (> 38°C), hypothermia (< 36°C), nausea, vomiting, hypertension, headache, shivering, tachycardia, arrhythmia, diarrhoea, and abdominal pain
- Patient-reported outcomes: maternal sense of well-being, satisfaction, and acceptability of the intervention
- Breastfeeding on discharge

Search methods for identification of studies

This Methods section is based on a standard template used by Cochrane Pregnancy and Childbirth group and the recent protocol adaption for multiple interventions suggested by Chaimani and colleagues (Chaimani 2017).

Electronic searches

We searched the Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (5 May 2020).

The Register is a database containing over 25,000 reports of controlled trials in the field of pregnancy and childbirth and it represents over 30 years of searching. For full current 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.

Briefly, 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 are 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 was 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 or Ongoing studies).

In addition, we searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports (5 May 2020) (see Appendix 1 for search methods used).

Searching other resources

We retrieved additional relevant references cited in papers identified through the above search strategy. We also searched for the full texts of trials initially identified as abstracts. For randomised trials published only as abstracts, we sought information from primary authors to investigate whether these studies met our eligibility criteria before including them. We did not apply any language or date restrictions.

Data collection and analysis

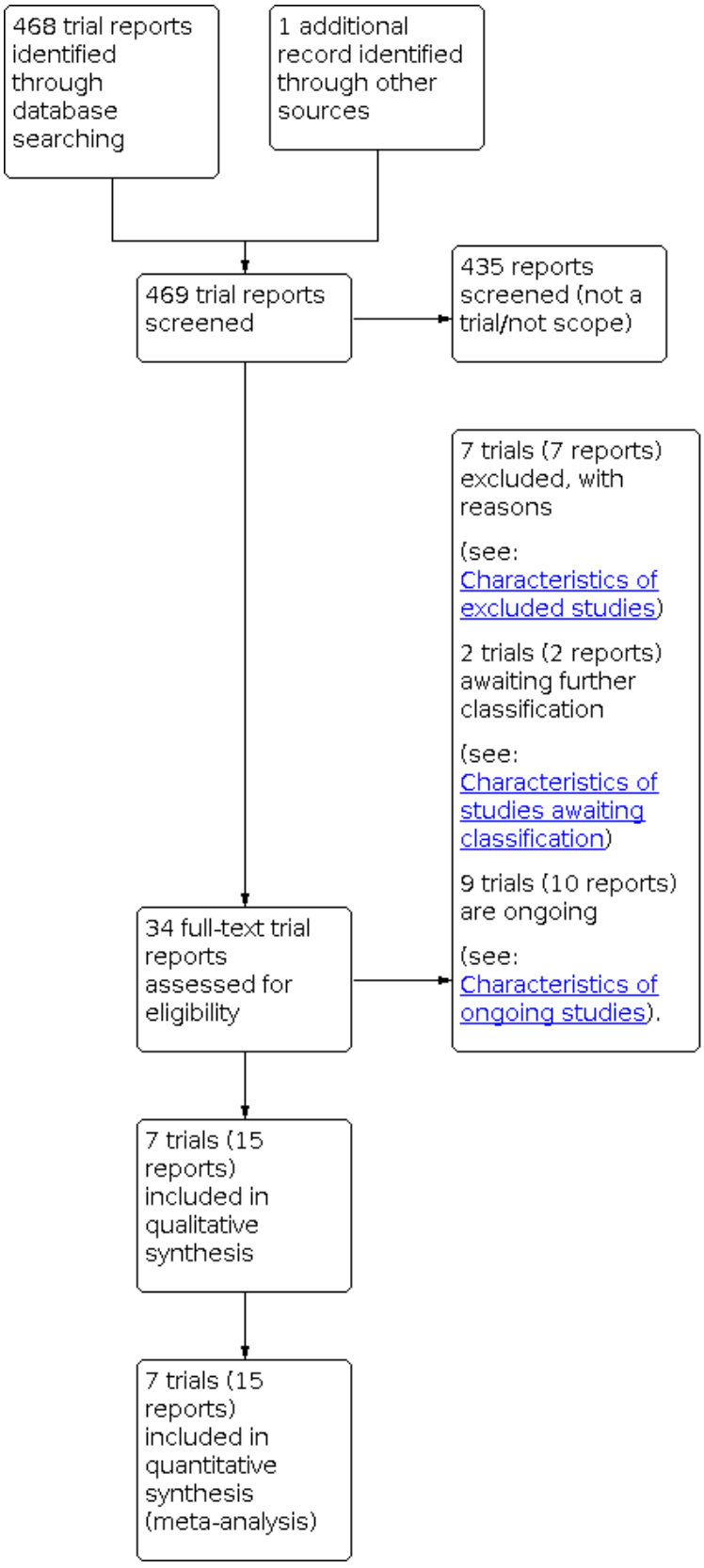
In the following sections we only report methods on standard pairwise and indirect treatment comparisons. Given that it was not possible to perform a network meta-analysis, all relevant methods are described in the appendix (see Appendix 2).

Selection of studies

At least two review authors retrieved and independently assessed for inclusion all potential studies identified as a result of the search strategy (WRPS, AP, SM). We resolved any disagreements through discussion or, if required, through consultation with a third person (IDG).

We created a study flow diagram to map out the number of records identified, included and excluded (Figure 1).

Figure 1. Study flow diagram.



Screening eligible studies for scientific integrity/trustworthiness

All studies meeting our inclusion criteria were also evaluated by two review authors against predefined criteria to select studies that, based on available information, were deemed to be sufficiently trustworthy to be included in the analysis. The criteria are as follows.

Research governance

- No prospective trial registration for studies published after 2010 without plausible explanation
- When requested, trial authors refuse to provide/share the protocol and/or ethics approval letter
- Trial authors refuse to engage in communication with the Cochrane Review authors
- Trial authors refuse to provide IPD data upon request with no justifiable reason

Baseline characteristics

- Characteristics of the study participants being too similar (distribution of mean (SD) excessively narrow or excessively wide, as noted by Carlisle 2017.

Feasibility

- Implausible numbers (e.g. 500 women with severe PPH recruited in 12 months)
- (Close to) zero losses to follow up without plausible explanation

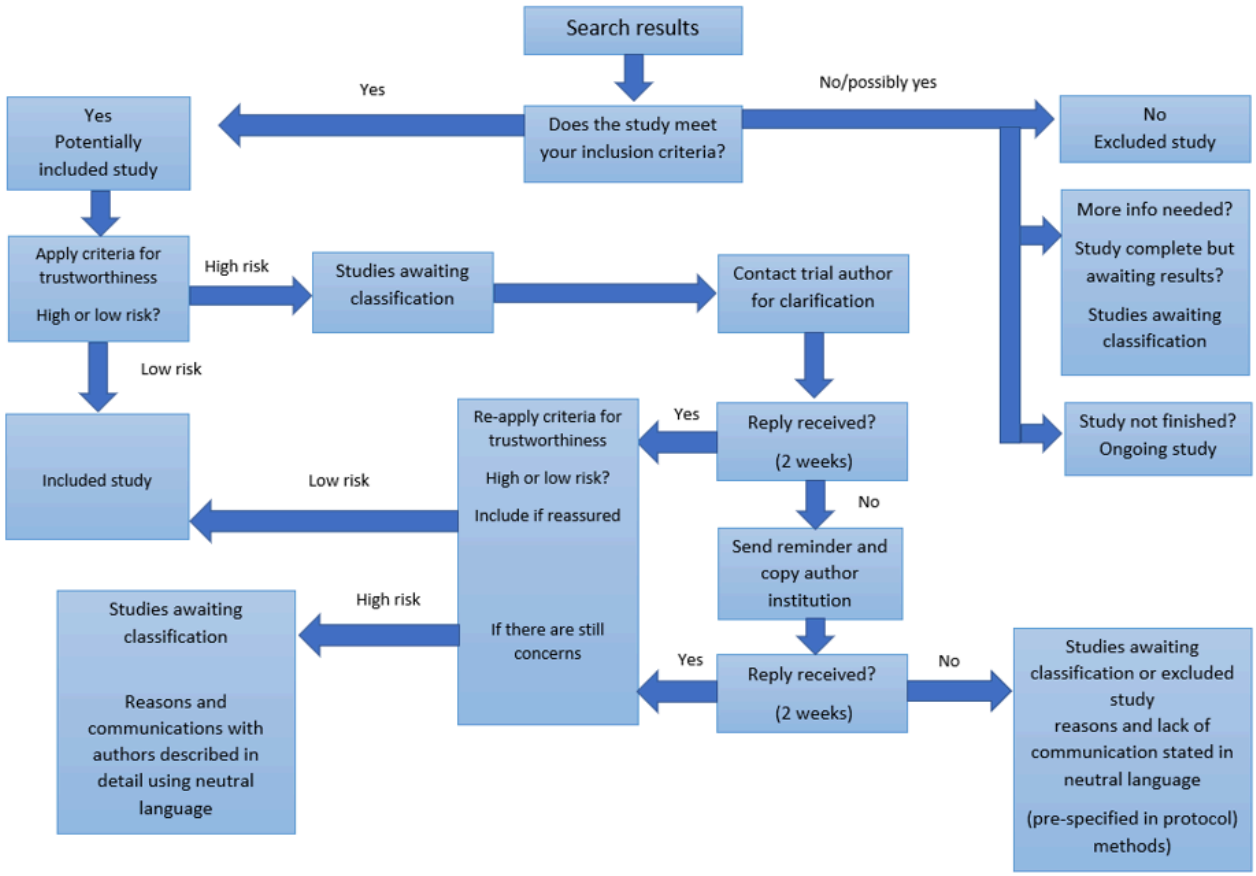
Results

- Implausible results (e.g. massive risk reduction for main outcomes with small sample size)
- Unexpectedly even numbers of women 'randomised' including a mismatch between the numbers and the methods, e.g. if they say no blocking was used but still end up with equal numbers, or they say they used blocks of four but the final numbers differ by six

Studies assessed as being potentially 'high risk' were not be included in the review. Where a study is classified as 'high risk' for one or more of the above criteria, we attempted to contact the study authors to address any possible lack of information/concerns. If adequate information remained unavailable, the study remained in 'awaiting classification' and the reasons and communications with the author (or lack of) described in detail.

The process is described fully in Figure 2.

Figure 2. Process for using the Cochrane Pregnancy and Childbirth criteria for assessing the trustworthiness of a study



Abstracts

Data from abstracts were only included if, in addition to the trustworthiness assessment, the study authors confirmed in writing that the data to be included in the review have come from the final analysis and will not change. If such information was not available/provided, the study remained in, 'awaiting classification' (as above).

Data extraction and management

We designed an electronic form to extract data. For eligible studies, at least two review authors independently extracted the data using a blank electronic form (WRPS, AP, SM). We resolved discrepancies through discussion or, if required, we consulted a third person (IDG). We entered data into the Review Manager software (RevMan 2014) and checked them for accuracy. When information was unclear, we attempted to contact the authors of the original reports to provide further details. We extracted the following data:

Methods

1. Study design
2. Sequence generation
3. Allocation sequence concealment
4. Blinding
5. Attrition
6. Study protocol and inconsistencies compared with the published report
7. Financial support and conflicts of interest
8. Other concerns about bias

Outcome data

From each included trial we extracted: the number of participants, the number of fetuses (singleton or multiple gestations), exclusion criteria from the trial, the interventions being compared along with any co-interventions, 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, and means and standard deviations per study arm for continuous outcomes).

Data on potential effect modifiers

In addition, from each included trial we extracted the following study, intervention and population characteristics that could act as effect modifiers.

1. Gestational age
2. Parity
3. Mode of delivery (vaginal or caesarean birth)
4. Prior risk of PPH (as defined by trialists and categorised as low, high or mixed)
5. Uterotonic administration prior to enrolment
6. Dosage, regimen, and route of administration (sublingual, oral, rectal, intramuscular, intravenous bolus and/or infusion)
7. Study setting (community or hospital)
8. Co-interventions such as tranexamic acid and uterine massage
9. Randomisation unit

Other data

From each included trial we extracted the following additional data.

1. Country or countries in which the study was performed
2. Year of publication and dates of recruitment
3. Type of publication (full text, abstract or unpublished data)
4. Trial registration reference

Assessment of risk of bias in included studies

At least two review authors (WRPS, AP) independently assessed the risk of bias of each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), modified as appropriate to the context of this review, and described below. We resolved any disagreements by discussion or by involving a third assessor (IDG).

(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 trial the method used to generate the allocation sequence and made an assessment of whether it should produce comparable groups.

We assessed the method as:

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

(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 affect 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 data were 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 not exceeding 10%);
- 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 (exclusions or attrition unreported).

(5) Selective reporting (checking for reporting bias)

We described for each included study any inconsistency between the prespecified study protocol (if available), the study methods described in the study report, and the results listed in the study report.

We assessed the methods as:

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

(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 (unspecified source of funding).

Another source of bias that we assessed was 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 measurement such as weighing swabs, measurements in drapes, volumetric assessment, tagged red cells, etc);
- high risk of other bias (subjective measurement such as visual or clinical estimation); or
- unclear risk of other bias (unspecified methods of measurement).

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For our primary outcomes, we combined quality items and judged trials as 'low risk of bias' if they were double-blind, had allocation concealment 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'.

Summary of findings

Each 'Summary of findings' table describes key features of the direct evidence relating to a single outcome, and there is one table for each of the critical outcomes of this review in accordance with the GRADE approach. These include the outcome of additional blood loss of 500 mL or more, the composite of death or severe morbidity, the use of additional uterotonics, additional blood loss of 1000 mL or more, blood transfusion or other blood products, and the side-effects of fever and vomiting.

We assessed the certainty of the direct evidence, and rated the evidence using the standard GRADE approach based on assessment of study design limitations, heterogeneity, imprecision, indirectness and publication bias (Higgins 2011). For each outcome of interest, on the corresponding network diagram we have displayed the GRADE assessment of the direct evidence for all available treatment comparisons. We also rated the certainty of the indirect evidence, where available, based on the lower of the certainty ratings of the two arms forming the dominant ‘first-order' loop in the network diagram for a specific outcome (Puhan 2014; Brignardello-Petersen 2018).

The certainty of evidence for each outcome was rated as ‘high', ‘moderate', ‘low', or ‘very low' in accordance with the GRADE approach: High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: 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 certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Measures of treatment effect

Relative treatment effects

We summarised the relative treatment effects for dichotomous outcomes with risk ratios (RRs) and for continuous outcomes as mean difference (MD) with 95% confidence intervals (CIs). Had different scales been used for continuous outcomes we would have used standardised mean differences (SMDs) with 95% CIs (Dias 2013).

Unit of analysis issues

Cluster-randomised trials

There were no cluster-randomised trials included in this review. We planned to include cluster-randomised trials in the analyses along with individually-randomised trials. We would have adjusted their standard errors using the methods described in the Cochrane Handbook, with an estimate of the intracluster correlation co-efficient (ICC) derived from the trial, or from a similar trial or from a study of a similar population (Higgins 2011). If we had used ICCs from other sources, we would have reported this and conducted sensitivity analyses to investigate the effects of variations in the ICC. We would have considered it reasonable to combine the results if there was little heterogeneity between the study designs and if the randomisation unit could not plausibly affect the effects of the interventions. However, we would have performed sensitivity analyses to assess the validity of such combination.

Cross-over trials

This type of trial is not appropriate for this intervention, and was not eligible for inclusion in the review.

Multi-arm trials

We did not find any multi-arm trials to include in this review. Multi-arm studies would have been included and treated as multiple independent comparisons in pairwise meta-analyses.

Dealing with missing data

For included studies we noted the levels of attrition (see also 'Incomplete outcome data' in Assessment of risk of bias in included studies).

For all outcomes, we carried out analyses, as far as possible, on a modified intention-to-treat basis, i.e. we attempted to include 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 reporting biases

We were not able to assess for reporting bias in view of the limited number of included trials. If there were at least 10 studies in the meta-analysis, we would have investigated reporting biases (such as publication bias) using funnel plots. The funnel plots would have been assessed visually for asymmetry.

Data synthesis

Methods for direct treatment comparisons

We performed standard pairwise meta-analyses using a random-effects model for every treatment comparison with at least two trials using Review Manager software (RevMan 2014). The random-effects method (DerSimonian 1986) was preferred as it incorporates an assumption that the different studies are estimating different, yet related, intervention effects. The standard errors of the study-specific estimates are adjusted to incorporate a measure of the extent of heterogeneity. This results to wider confidence intervals in the presence of heterogeneity, and corresponding claims of statistical significance are more conservative.

Methods for indirect treatment comparisons

We were able to use the method described by Bucher to produce indirect comparisons for the direct interest uterotonic agents and outcomes (misoprostol plus oxytocin versus misoprostol via oxytocin) (Bucher 1997). The indirect comparisons were estimated using Excel as described by Tobias (Tobias 2014).

Assessment of statistical heterogeneity

Assumptions when estimating heterogeneity

In standard pairwise meta-analyses we estimated the heterogeneity for each comparison.

Measures and tests for heterogeneity

We assessed statistically the presence of heterogeneity within each pairwise comparison using the I^2 statistic and its 95% CI that measures the percentage of variability that cannot be attributed to random error. The certainty of the evidence was downgraded for inconsistency where $I^2 \geq 60\%$.

Investigation of heterogeneity

We planned to investigate heterogeneity by carrying out a number of pre-specified subgroup analyses. Only a few studies were included in this review and for most outcomes only one or two studies contributed data or heterogeneity was low. Although, data were not currently available for many of the subsets of participants, we will assess for possible effect modifiers in future updates (see Appendix 2).

Subgroup analysis

Regardless of heterogeneity, for the primary outcomes, we would have performed the following subgroup analyses by evaluating the relative effects and assessment of model fit.

- Mode of delivery (vaginal versus caesarean delivery).
- Prior PPH risk (low versus high risk).
- Setting (hospital versus community births).
- Intervention: dosage and route.
- Uterotonic administration prior to enrolment.
- Co-interventions (e.g. tranexamic acid, uterine massage).

Sensitivity analysis

For the primary outcomes we would have performed the following sensitivity analyses.
• Overall risk of bias.
• Funding source.
• Objective versus subjective assessment of blood loss.
• Randomisation unit (cluster versus individual).
Differences would have been assessed by evaluating the relative effects and assessment of model fit.

RESULTS

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-Analysis) flow diagram (Figure 1).

Our search strategy retrieved in total 469 records from which 435 were screened and excluded as they were not within the scope of this review. From the 34 records remaining, we examined the full text and decided to include in the final analysis seven trials from 15 records (for details see Characteristics of included studies). Seven records were excluded because they did not meet the inclusion criteria (for details see Characteristics of excluded studies), 10 records (nine trials) were listed as ongoing (for details see Characteristics of ongoing studies) and two are awaiting classification (for details see Characteristics of studies awaiting classification).

Screening eligible studies for scientific integrity/ trustworthiness

All potentially eligible studies were assessed for scientific integrity and trustworthiness. One trial (Maged 2016) remains in Characteristics of studies awaiting classification pending further clarification and data from the study authors before deciding whether we should include this trial in future updates. Maged 2016 was a small trial conducted in Egypt comparing carbetocin with oxytocin for treating postpartum haemorrhage (PPH). Another trial remains in awaiting classification pending full-text publication (NCT01116050).

Included studies

This review includes seven two-arm randomised trials, published between 2001 and 2010, involving 3738 women. All studies were reported in English and were conducted in hospital settings across 10 countries: Argentina, Burkina Faso, Ecuador, Egypt, Gambia, Pakistan, South Africa, Thailand, Turkey, and Vietnam. The included trials included a median of 534 participants (interquartile range (IQR) 61 to 1422).

Randomised women gave birth vaginally (3674 women), except in one trial, where women gave birth either vaginally or by caesarean section (64 women). In all included studies women were judged to be at mixed risk for PPH (including women at both low and high risk for PPH).

Across all seven trials (14 trial arms) the following agents were used:

- six trial arms (43%) used oxytocin*;
- four trial arms (29%) used misoprostol plus oxytocin;
- three trial arms (21%) used misoprostol;
- one trial arm (7%) used Syntometrine® (oxytocin and ergometrine) plus oxytocin.

*Not all trials were explicit about administering oxytocin to all women. For example, in Hofmeyr 2004, it was stated that oxytocin was administered by an intravenous infusion but some woman received ergometrine plus oxytocin. In Walraven 2004, administration of oxytocics was not further specified. For Widmer 2010 it is stated that in most cases 10 International Units (IU) of oxytocin was administered intramuscularly or by a slow intravenous injection. See Characteristics of included studies for details.

Excluded studies

We excluded seven trials (for details see Characteristics of excluded studies). Four of the excluded studies investigated ineligible interventions and three had ineligible designs.

Ongoing studies

We contacted the authors of six of the ongoing trials which are reported to have finished recruitment to obtain data, but no additional information was made available to us.

Risk of bias in included studies

We present summaries of the methodological quality of the included studies for each domain assessed across all studies (Figure 3) and for each included study (Figure 4).

Figure 3. 'Risk of bias' graph: Review authors' judgements about each risk of bias item, presented as percentages across all included studies.

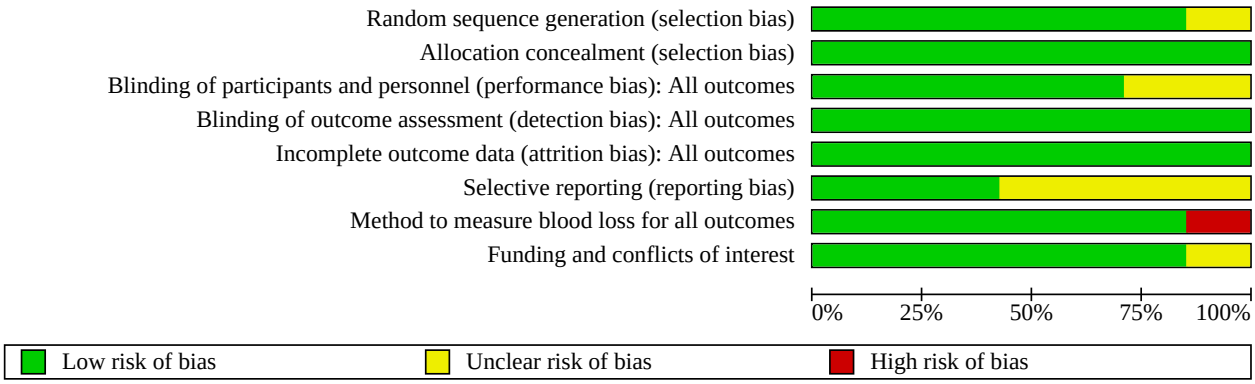
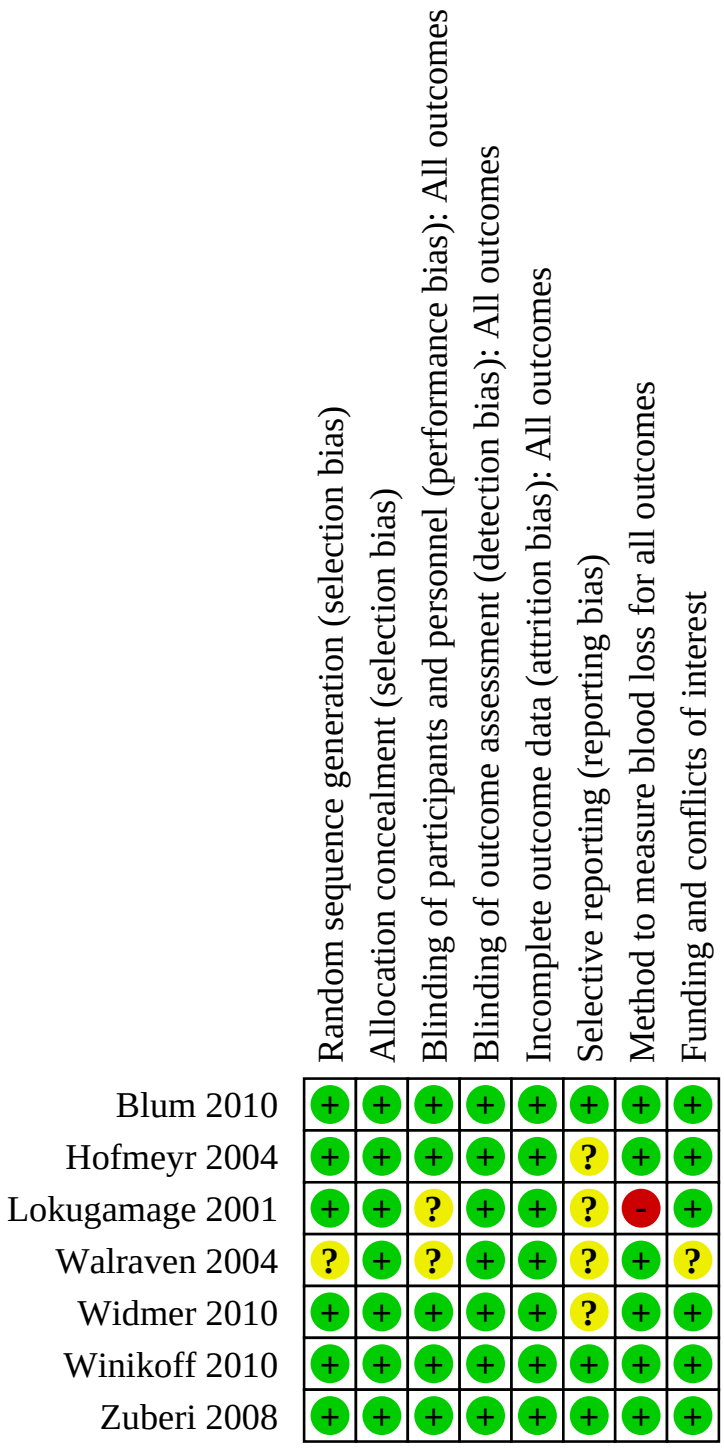


Figure 4. 'Risk of bias' summary: Review authors' judgements about each risk of bias item, for each included study.



Allocation

No trials were excluded due to sequence generation concerns. Six trials (86%) used an adequate method to generate the random sequence and were judged to be at low risk of bias. Only one trial (14%) did not provide enough evidence to judge the method of random sequence generation and it was judged to have an unclear risk of bias (Walraven 2004). All trials reported adequate methods for allocation concealment and were judged to be at low risk of bias.

Blinding

In total, five out of the seven included trials (71%) reported adequate methods for blinding both participants and personnel to treatment allocation and were judged to be at a low risk of bias. Two trials (29%) did not provide enough information to assess the blinding of participants and personnel and the risk of bias was judged to be unclear (Lokugamage 2001; Walraven 2004). All trials reported adequate methods for blinding the assessment of the primary outcomes and were judged to be at a low risk of detection bias.

Incomplete outcome data

All trials were judged to be at a low risk of attrition bias, since missing data were balanced across study arms and did not exceed 10%.

Selective reporting

Only three out of the seven included trials (42%) pre-specified all outcomes in publicly available protocols and were judged to be at a low risk of bias. Two trials (29%) reported all outcomes as specified in their published protocols, but the protocols were registered retrospectively (Hofmeyr 2004; Widmer 2010). These trials were judged to be at an unclear risk of bias. For the remaining two trials (29%), the protocol was unavailable for verification and they were also judged to be at unclear risk of bias (Lokugamage 2001; Walraven 2004).

Other potential sources of bias

Six trials (86%) used 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. One trial (14%) were judged to be at high risk of bias for measuring blood loss, since investigators appraised blood loss by visual estimation (Lokugamage 2001).

Six trials (86%) were judged to be at a low risk of bias regarding funding or potential conflicts of interest. There was one trial (14%) that 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 (Walraven 2004).

Effects of interventions

See: **Summary of findings 1** Additional blood loss of 500 mL or more; **Summary of findings 2** Composite of death or severe morbidity; **Summary of findings 3** Use of additional uterotonics; **Summary of findings 4** Additional blood loss of 1000 mL or more; **Summary of findings 5** Blood transfusion or other blood products; **Summary of findings 6** Side effects: fever; **Summary of findings 7** Side effects: vomiting

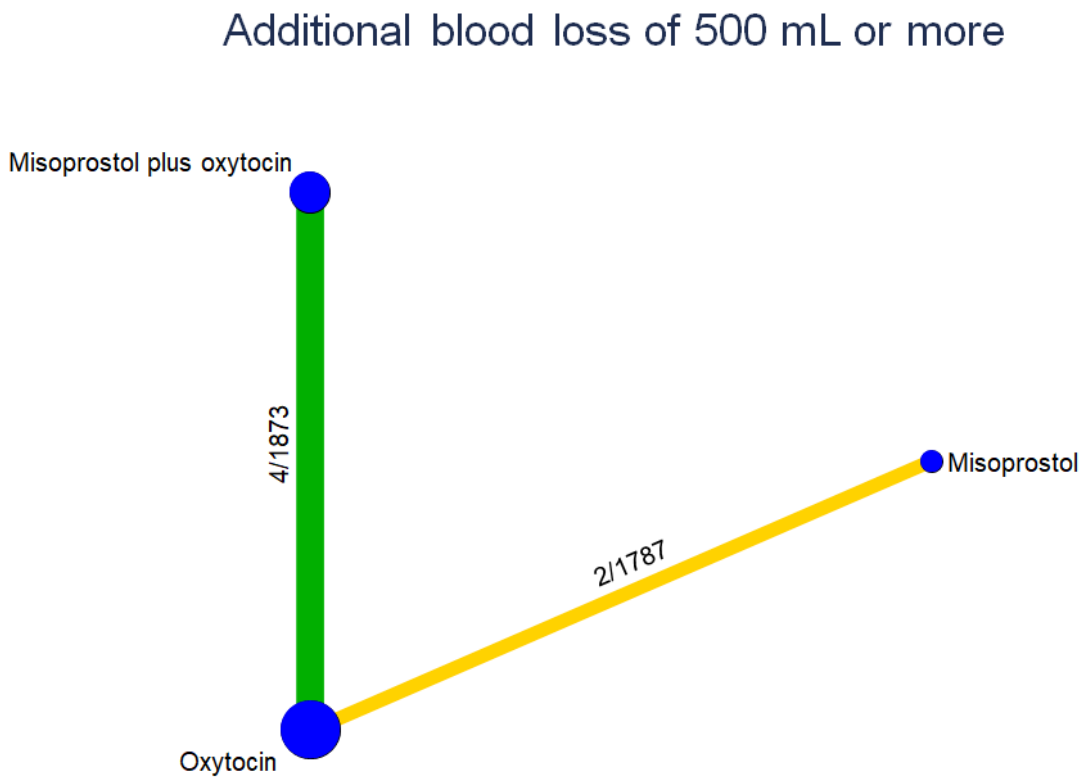
Please note that all of the analyses presented in the Data and analyses section relate to the 'direct evidence' and were used to grade the evidence. The analyses for the only indirect comparison of misoprostol versus misoprostol plus oxytocin are described narratively and included in the 'Summary of findings' tables, where available. For each outcome we present the network diagrams displaying the available comparisons and the grading of the direct evidence.

Primary outcomes

Additional blood loss of 500 mL or more

The network diagram for additional blood loss of 500 mL or more is presented in Figure 5.

Figure 5. Network Diagram for additional blood loss of 500 mL or more after recruitment to the trial and until cessation of active bleeding. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. 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 light green for moderate-certainty evidence and orange for low-certainty evidence.



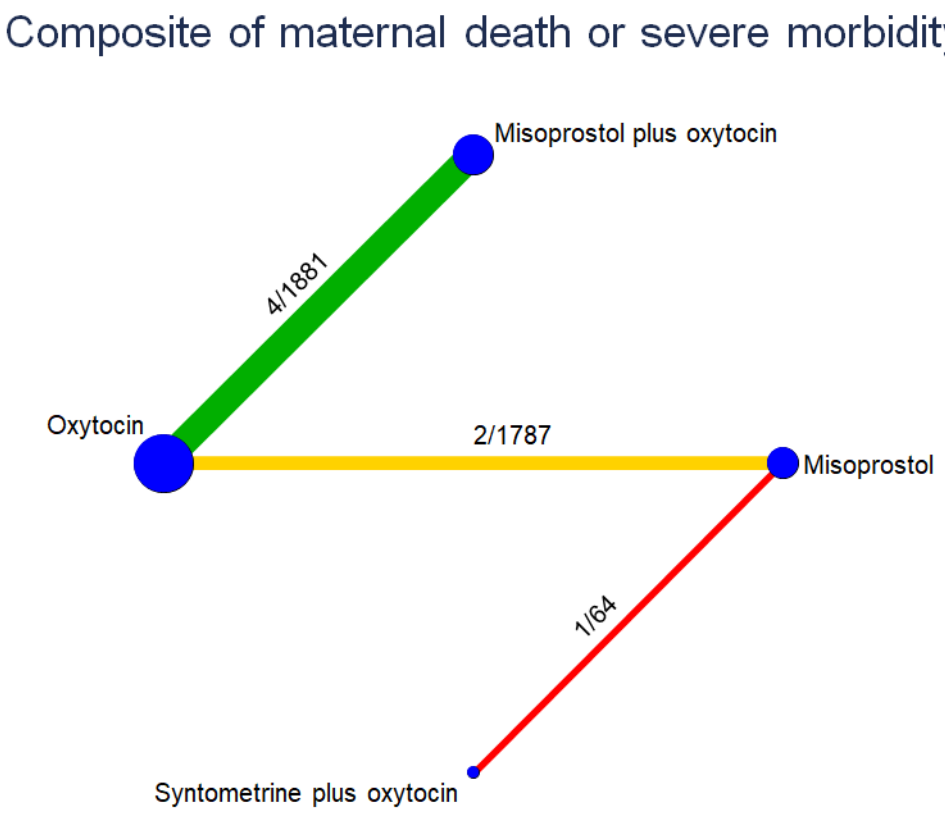
There were two direct comparisons for this outcome. In the first comparison, misoprostol was compared with oxytocin (2 trials, 1787 women) and in the second one, misoprostol plus oxytocin was compared with oxytocin alone (4 trials, 1873 women). The relative effects from pairwise meta-analysis comparing misoprostol with oxytocin are compatible with a wide range of treatment effects for additional blood loss of 500 mL or more (risk ratio (RR) 1.66, 95% confidence interval (CI) 0.69 to 4.02), low-certainty evidence, Summary of findings 1; Analysis 1.1). For the comparison of a combination of misoprostol with oxytocin versus oxytocin alone, we cannot rule out an important benefit for this outcome (RR 0.84, 95% CI 0.66 to 1.06, moderate-certainty evidence, Summary of findings 1; Analysis 3.1).

Although it was not possible to perform a network meta-analysis, we were able to compare misoprostol plus oxytocin combination with misoprostol alone through the common comparator of oxytocin. This indirect comparison suggests that misoprostol plus oxytocin combination is compatible with a wide range of treatment effects for this outcome compared with misoprostol alone (RR 0.51, 95% CI 0.20 to 1.26, low-certainty evidence, Table 1).

Composite of death or severe morbidity

The network diagram for the composite outcome of death or major morbidity is presented in Figure 6.

Figure 6. Network Diagram for the composite outcome of maternal death or severe morbidity. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. 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 light green for moderate-certainty evidence, orange for low-certainty evidence and red for very low-certainty evidence.



There were three available comparisons for this outcome. Misoprostol was compared with oxytocin (2 trials, 1787 women), misoprostol was compared with Syntometrine® plus oxytocin (1 trial, 64 women), and the misoprostol plus oxytocin combination was compared with oxytocin alone (4 trials, 1881 participants). For the comparison of misoprostol versus oxytocin, only one of the two trials reported events and contributed to the summary effect estimate. Based on the results from this single study, the comparison of misoprostol versus oxytocin is compatible with a wide range of treatment effects (1 trial, 809 women, RR 1.98, 95% CI 0.36 to 10.72, low-certainty evidence, Summary of findings 2; Analysis 1.2). When combining misoprostol with oxytocin, we cannot rule out important effects either way, compared with using oxytocin alone (4 trials, 1881 women, RR 1.09, 95% CI 0.35 to 3.39, moderate-certainty evidence, Summary of findings 2; Analysis 3.2). Given that the certainty of the evidence was very low for misoprostol versus Syntometrine® plus oxytocin, these effects remain unclear (Summary of findings 2; Analysis 2.1).

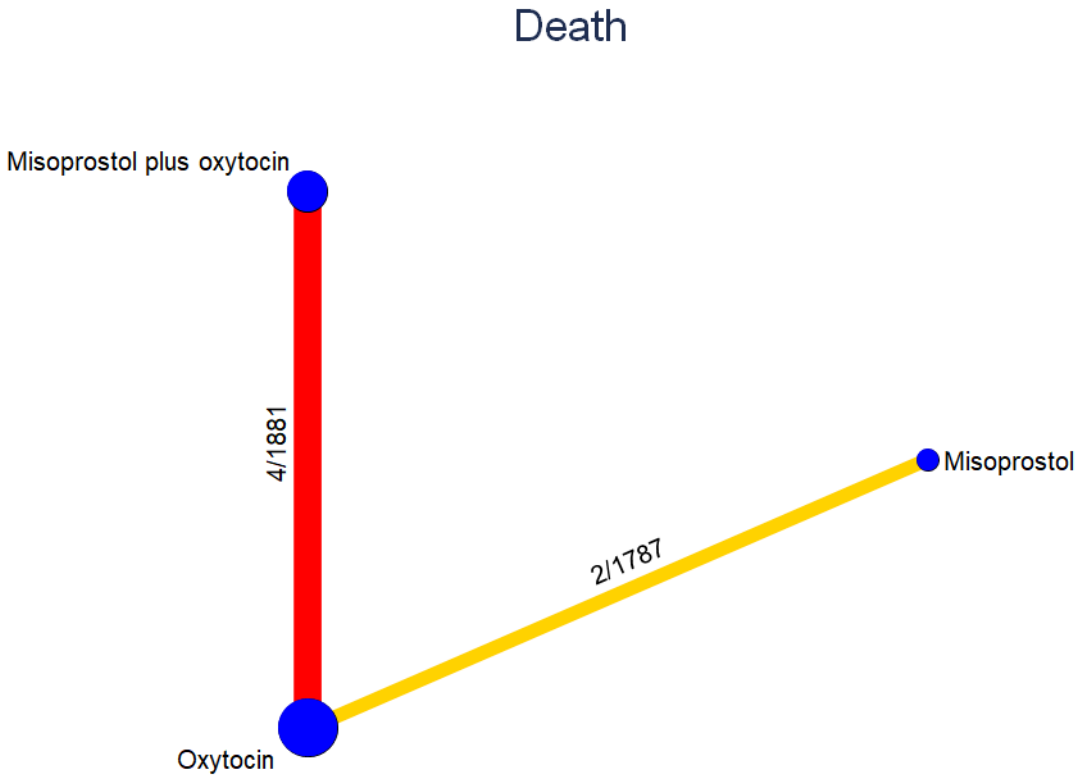
Indirect evidence also suggests that misoprostol plus oxytocin compared with misoprostol is compatible with a wide range of treatment effects for this composite outcome (RR 0.55, 95% CI 0.07 to 4.24, low-certainty evidence, Table 1).

Secondary outcomes

Death

The network diagram for death is presented in Figure 7.

Figure 7. Network Diagram for death. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. 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 orange for low-certainty evidence and red for very low-certainty evidence.

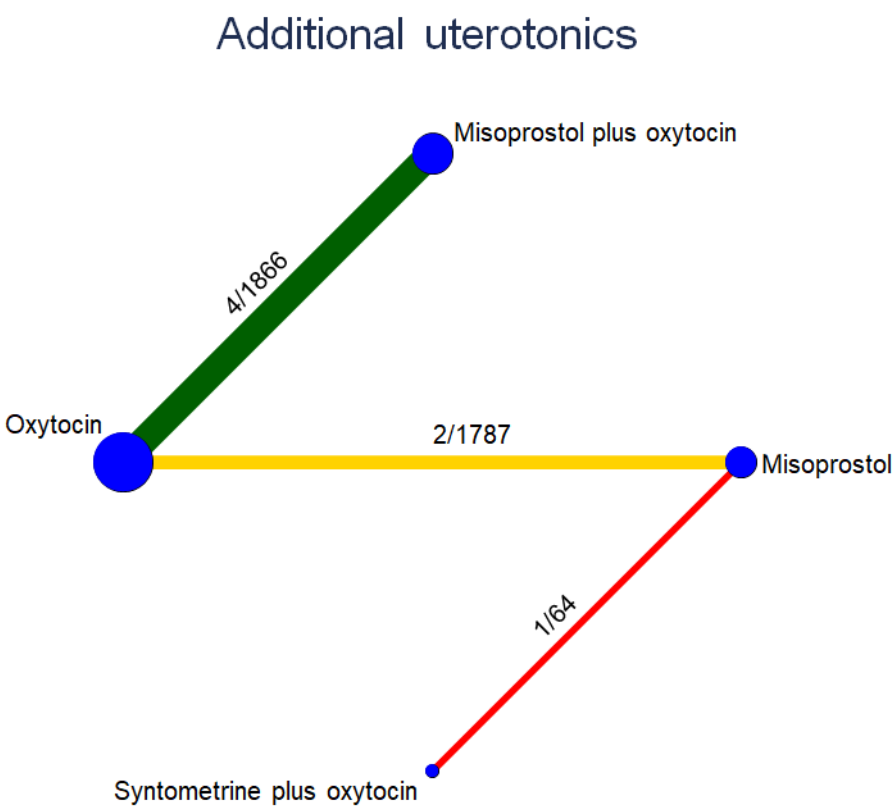


There were two available comparisons for this outcome. Misoprostol was compared with oxytocin (2 trials, 1787 women) and misoprostol plus oxytocin was compared with oxytocin alone (4 trials, 1881 women). For the comparison of misoprostol versus oxytocin, only one of the two trials reported events and contributed to the summary effect estimate - based on the results from this single study with events, when misoprostol is compared with oxytocin, we cannot rule out important effects either way for the outcome of maternal death (1 trial, 809 women, RR 0.99, 95% CI 0.06 to 15.74, low-certainty evidence, Analysis 1.3). The effects for misoprostol plus oxytocin combination compared with oxytocin alone were uncertain (Analysis 3.3).

Use of additional uterotonics

The network diagram for the use of additional uterotonics is presented in Figure 8.

Figure 8. Network Diagram for additional uterotonics. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. 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 dark green for high-certainty evidence, orange for low-certainty evidence and red or very low-certainty evidence.



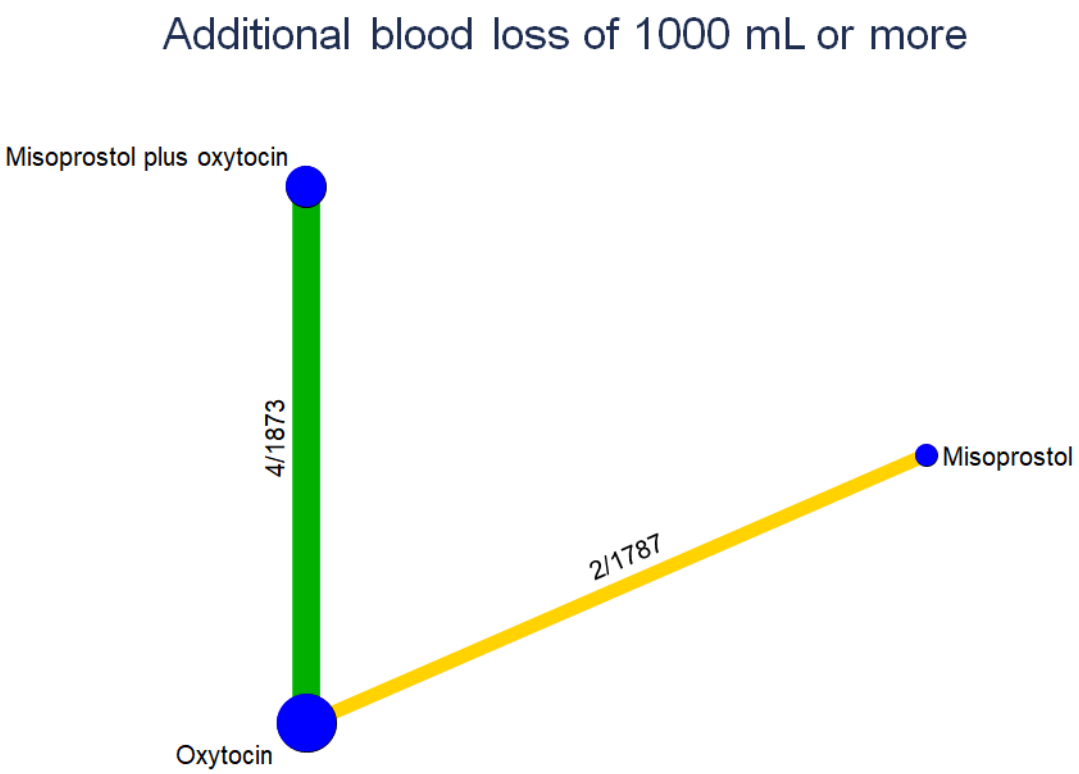
There were three available comparisons for this outcome; misoprostol was compared with oxytocin (2 trials, 1787 women), misoprostol was compared with Syntometrine® plus oxytocin (1 trial, 64 women), and misoprostol plus oxytocin was compared with oxytocin alone (4 trials, 1866 women). Based on the relative effects from pairwise meta-analysis, misoprostol is compatible with a wide range of treatment effects compared with oxytocin (RR 1.30, 95% CI 0.57 to 2.94, low-certainty evidence, Summary of findings 3; Analysis 1.4). Misoprostol administered together with oxytocin makes little or no difference to this outcome compared with oxytocin alone (RR 0.99, 95% CI 0.94 to 1.05, high-certainty evidence, Summary of findings 3; Analysis 3.4). The effects for misoprostol compared with Syntometrine® plus oxytocin remained unclear (Summary of findings 3; Analysis 2.2).

Indirect evidence suggests that the comparison of misoprostol plus oxytocin versus misoprostol alone is compatible with a wide range of treatment effects for the use of additional uterotonics (RR 0.76, 95% CI 0.33 to 1.73, low-certainty evidence, Table 1).

Additional blood loss of 1000 mL or more

The network diagram for additional blood loss of 1000 mL or more is presented in Figure 9.

Figure 9. Network Diagram for additional blood loss of 1000 mL or more after recruitment to the trial and until cessation of active bleeding. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. 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 light green for moderate-certainty evidence and orange for low-certainty evidence.



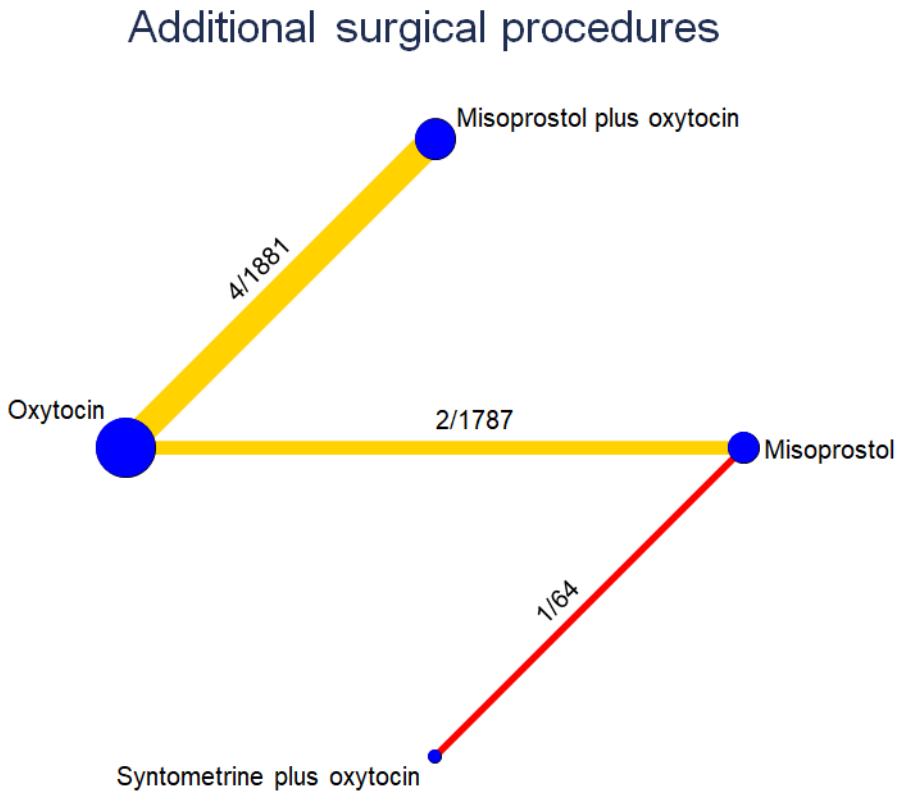
There were two available comparisons for this outcome; misoprostol was compared with oxytocin (2 trials, 1787 women) and misoprostol plus oxytocin was compared with oxytocin alone (4 trials, 1873 women). Based on the relative effects from pairwise meta-analysis, misoprostol may increase the incidence of additional blood loss of 1000 mL or more (RR 2.57, 95% CI 1.00, to 6.64, low-certainty evidence, Summary of findings 4; Analysis 1.5). For the comparison of misoprostol plus oxytocin versus oxytocin alone, only three of the four trials reported events and contributed to the summary effect estimate. When adding misoprostol to the conventional treatment with oxytocin alone, we cannot rule out important effects either way (3 trials, 1814 women, RR 0.76, 95% CI 0.43 to 1.34, moderate-certainty evidence, Summary of findings 4; Analysis 3.5).

Indirect evidence suggests that misoprostol plus oxytocin compared with misoprostol alone may reduce the risk for additional blood loss of 1000 mL or more (RR 0.30, 95% CI 0.10 to 0.89, low-certainty evidence, Table 1).

Additional surgical procedures (e.g. hysterectomy, balloon insertion, pack insertion, arterial ligation, embolisation, and compression sutures)

The network diagram for the additional surgical procedures is presented in Figure 10.

Figure 10. Network Diagram for additional surgical procedures. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. 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 orange for low-certainty evidence and red for very low-certainty evidence.



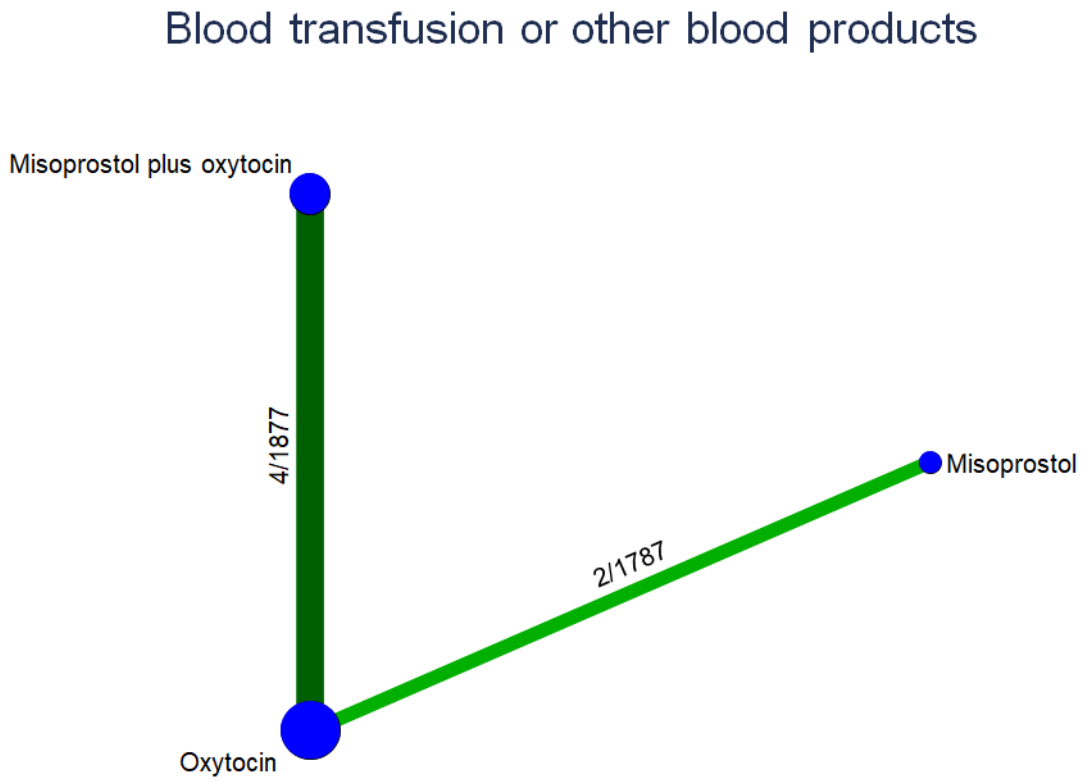
There were three available comparisons for this outcome; misoprostol was compared with oxytocin (2 trials, 1787 women), misoprostol was compared with Syntometrine® plus oxytocin (1 trial, 64 women), and misoprostol plus oxytocin was compared with oxytocin alone (4 trials, 1881 women).

For the comparison of misoprostol versus oxytocin, two trials reported this outcome, but only one trial reported events and contributed to the summary effect estimate. Based on the results from this single study, the comparison of misoprostol versus oxytocin is compatible with a wide range of treatment effects (1 trial, 809 women, RR 1.10, 95% CI 0.45 to 2.67, low-certainty evidence, Analysis 1.6). For the same outcome, the comparison of misoprostol plus oxytocin versus oxytocin alone is similarly compatible with a wide range of treatment effects (RR 0.65, 95% CI 0.21 to 2.00, low-certainty evidence, Analysis 3.6). The evidence for misoprostol versus Syntometrine® plus oxytocin was of very low-certainty evidence, and thus these effects remained unclear (Analysis 2.3).

Blood transfusion or other blood products

The network diagram for blood transfusion or other blood products is presented in Figure 11.

Figure 11. Network Diagram for blood transfusion or other blood products. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. 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 dark green for high-certainty evidence and light green for moderate-certainty evidence.



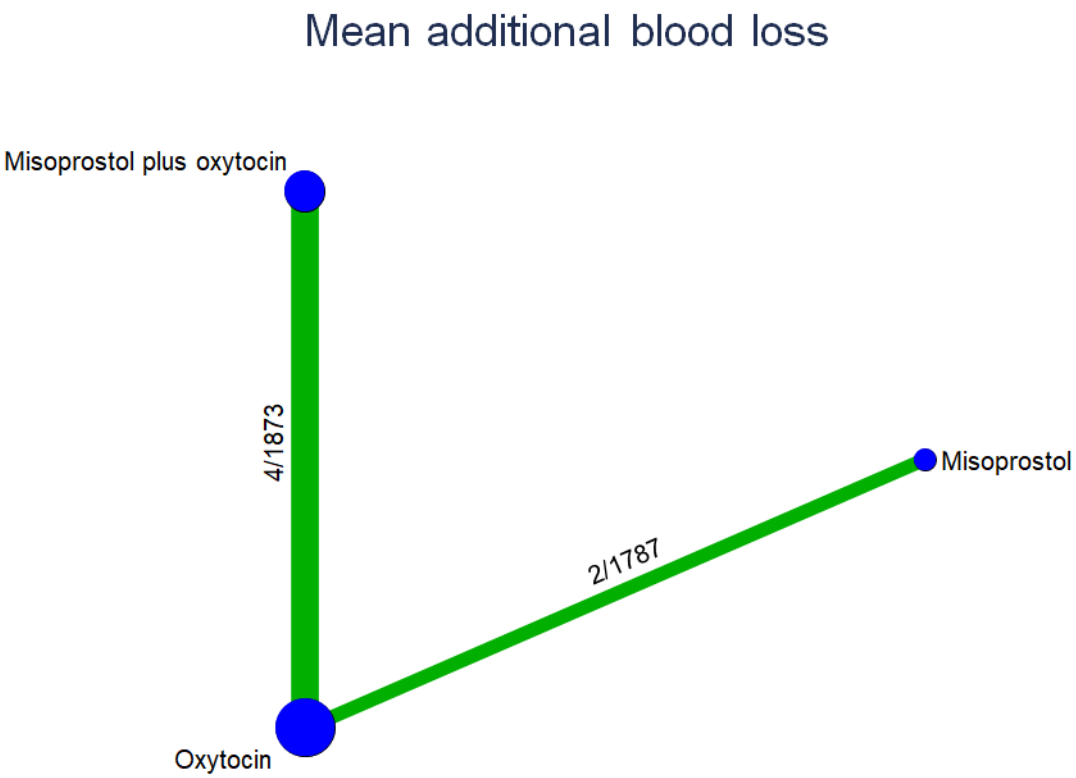
There were two available comparisons for this outcome; misoprostol was compared with oxytocin (2 trials, 1787 women) and misoprostol plus oxytocin was compared with oxytocin alone (4 trials, 1877 women). Based on the relative effects from pairwise meta-analysis, the administration of misoprostol probably increases the need for blood transfusion, compared with oxytocin (RR 1.47, 95% CI 1.02 to 2.14, moderate-certainty evidence, Summary of findings 5; Analysis 1.7). Adding misoprostol to conventional treatment with oxytocin makes little or no difference to this outcome compared with oxytocin alone (RR 0.95, 95% CI 0.77 to 1.17, high-certainty evidence, Summary of findings 5; Analysis 3.7).

Indirect evidence suggests that misoprostol plus oxytocin compared with misoprostol alone probably reduces the risk for blood transfusion (RR 0.65, 95% CI 0.42 to 0.99, moderate-certainty evidence, Table 1).

Mean additional blood loss (mL)

The network diagram for mean blood loss (mL) is presented in Figure 12.

Figure 12. Network Diagram for mean additional blood loss. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. 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 light green for moderate-certainty evidence.

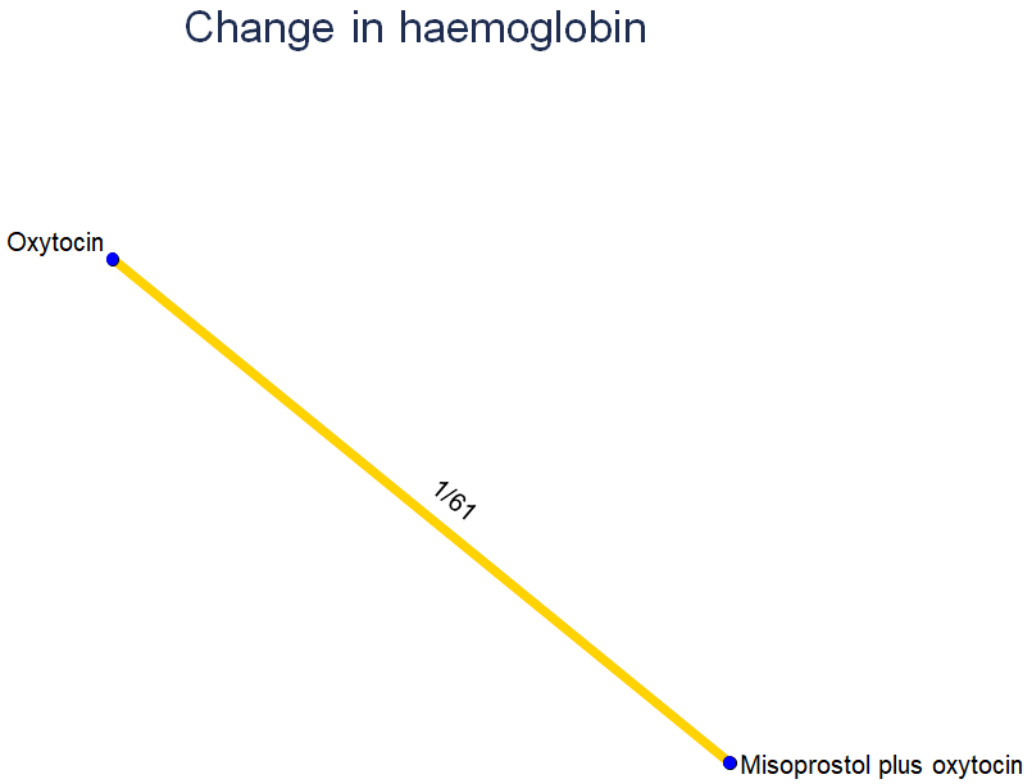


There were two available comparisons for this outcome; misoprostol was compared with oxytocin (2 trials, 1787 women) and misoprostol plus oxytocin was compared with oxytocin alone (4 trials, 1873 women). Based on the relative effects from pairwise meta-analysis, mean blood loss is probably slightly increased among women receiving misoprostol compared with those given oxytocin (mean difference (MD) 42.85 mL higher, 95% CI 16.79 mL higher to 68.90 mL higher, moderate-certainty evidence, Analysis 1.8). Misoprostol plus oxytocin probably makes little or no difference to the mean additional blood loss after recruitment compared with oxytocin alone (MD 14.59 mL lower, 95% CI 38.47 mL lower to 9.30 mL higher, moderate-certainty evidence, Analysis 3.8).

Change in haemoglobin (g/L)

The network diagram for change in haemoglobin (g/L) is presented in Figure 13.

Figure 13. Network Diagram for change in haemoglobin. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. 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 orange for low-certainty evidence.

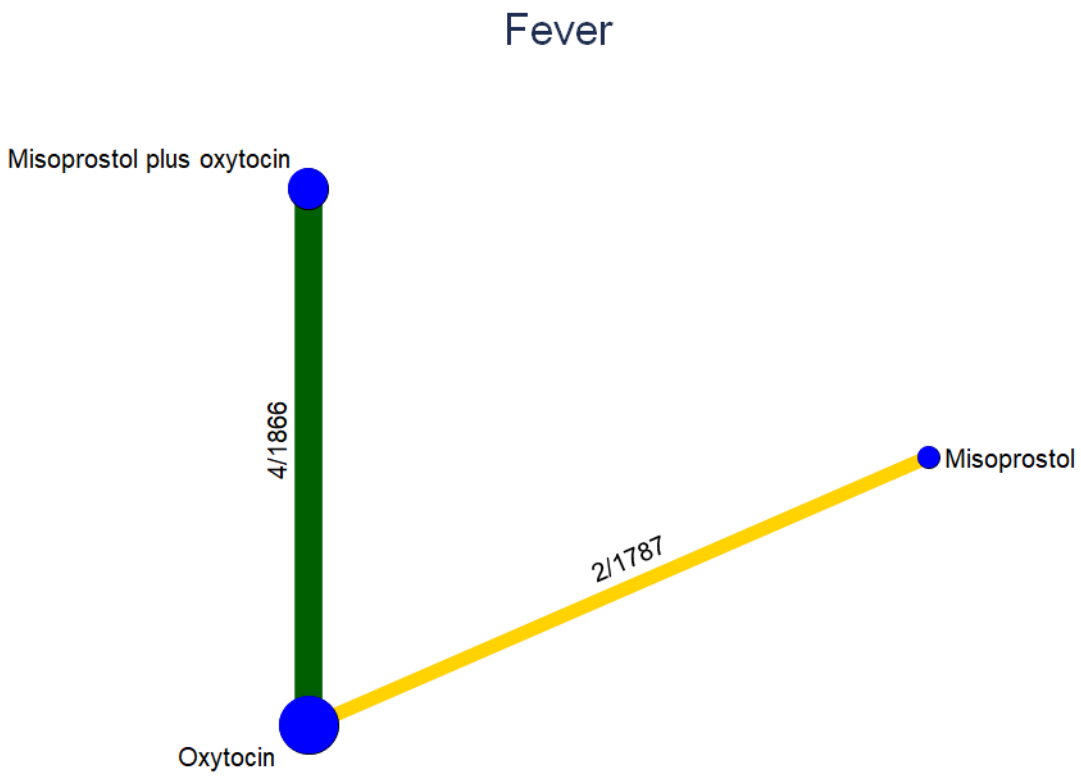


There was a single comparison available for this outcome; misoprostol plus oxytocin was compared with oxytocin alone (1 trial, 61 women). Based on the results from this single study, misoprostol plus oxytocin may make little or no difference to this outcome compared with oxytocin alone (MD 2.00 g/L lower, 95% CI 8.29 g/L lower to 4.29 g/L higher, low-certainty evidence, Analysis 3.9).

Side-effects: fever (temperature above 38°C)

The network diagram for fever is presented in Figure 14.

Figure 14. Network Diagram for fever. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. 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 dark green for high-certainty evidence and orange for low-certainty evidence.



There were two available comparisons for this outcome; misoprostol was compared with oxytocin (2 trials, 1787 women) and misoprostol plus oxytocin was compared with oxytocin alone (4 trials, 1866 women). Based on the relative effects from pairwise meta-analysis, misoprostol is compatible with a wide range of treatment effects for this outcome compared with oxytocin (RR 3.43, 95% CI 0.65 to 18.18, low-certainty evidence, Summary of findings 6; Analysis 1.9). However, adding misoprostol to conventional treatment with oxytocin increases the incidence of fever compared with oxytocin alone (RR 3.07, 95% CI 2.62 to 3.61, high-certainty evidence, Summary of findings 6; Analysis 3.10).

Based on indirect evidence, we cannot rule out important effects either way for the incidence of fever, when misoprostol plus oxytocin combination is compared with misoprostol alone (RR 0.90, 95% CI 0.17 to 4.77, low-certainty evidence, Table 1).

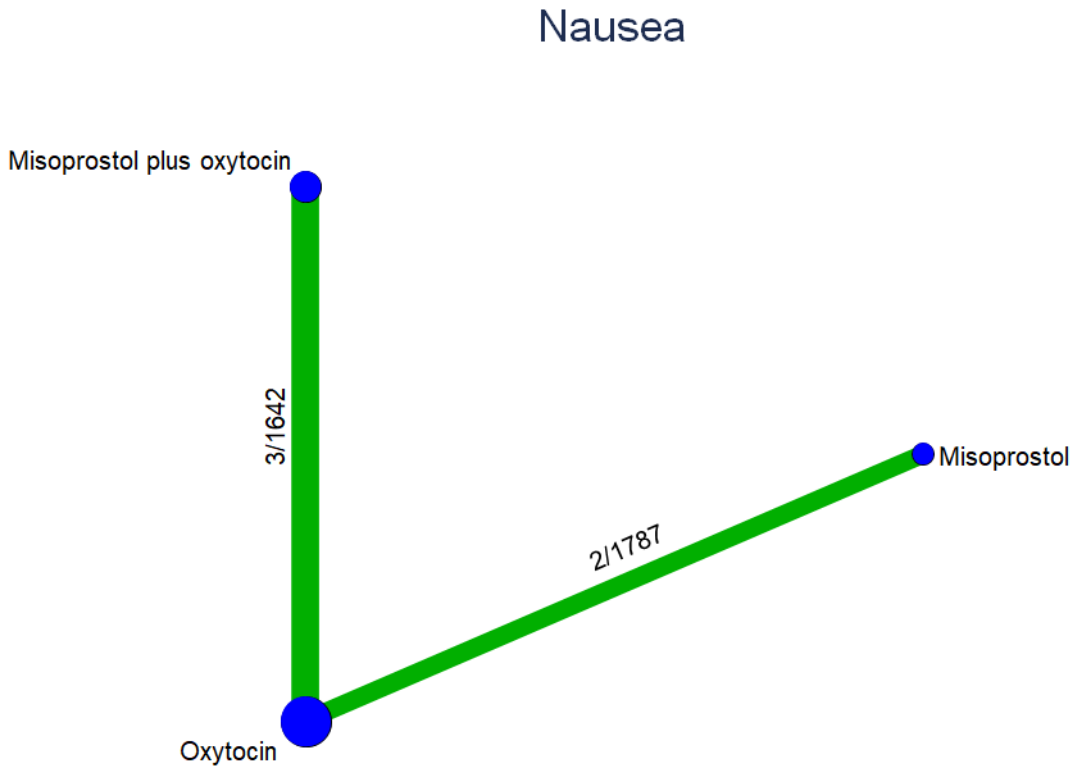
Side-effects: hypothermia (temperature below 36°C)

Not reported.

Side-effects: nausea

The network diagram for nausea is presented in Figure 15.

Figure 15. Network Diagram for nausea. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. 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 light green for moderate-certainty evidence.

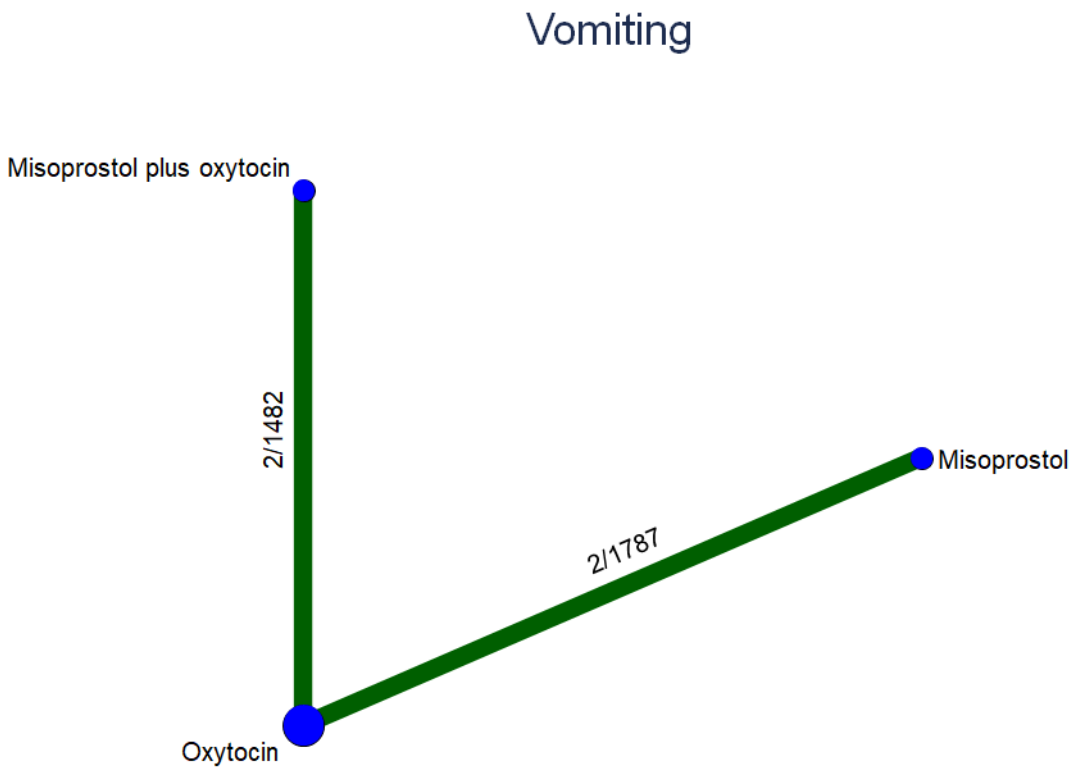


There were two available comparisons for this outcome; misoprostol was compared with oxytocin (2 trials, 1787 women) and misoprostol plus oxytocin was compared with oxytocin alone (3 trials, 1642 women). Based on the relative effects from pairwise meta-analysis, misoprostol probably makes little or no difference to women's experience of nausea compared with oxytocin (RR 0.99, 95% CI 0.70 to 1.39, moderate-certainty evidence, Analysis 1.10). Additionally, misoprostol plus oxytocin probably makes little or no difference to the incidence of nausea compared with oxytocin alone (RR 1.19, 95% CI 0.84 to 1.68, moderate-certainty evidence, Analysis 3.11).

Side-effects: vomiting

The network diagram for vomiting is presented in Figure 16.

Figure 16. Network Diagram for vomiting. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. 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 dark green for high-certainty evidence.



There were two available comparisons for this outcome; misoprostol was compared with oxytocin (2 trials, 1787 women) and misoprostol plus oxytocin was compared with oxytocin alone (2 trials, 1482 participants). Based on the relative effects from pairwise meta-analysis, the administration of misoprostol results in a large increase in vomiting compared with oxytocin treatment (RR 2.47, 95% CI 1.37 to 4.47, high-certainty evidence, Summary of findings 7; Analysis 1.11). Additionally, administering misoprostol together with oxytocin also results in a large increase in this outcome compared with the administration of oxytocin alone (RR 1.85, 95% CI 1.16 to 2.95, high-certainty evidence, Summary of findings 7; Analysis 3.12).

Indirect evidence suggests that misoprostol plus oxytocin compared with misoprostol alone does not increase the risk for vomiting (RR 0.75, 95% CI 0.35 to 1.59, high-certainty evidence, Table 1).

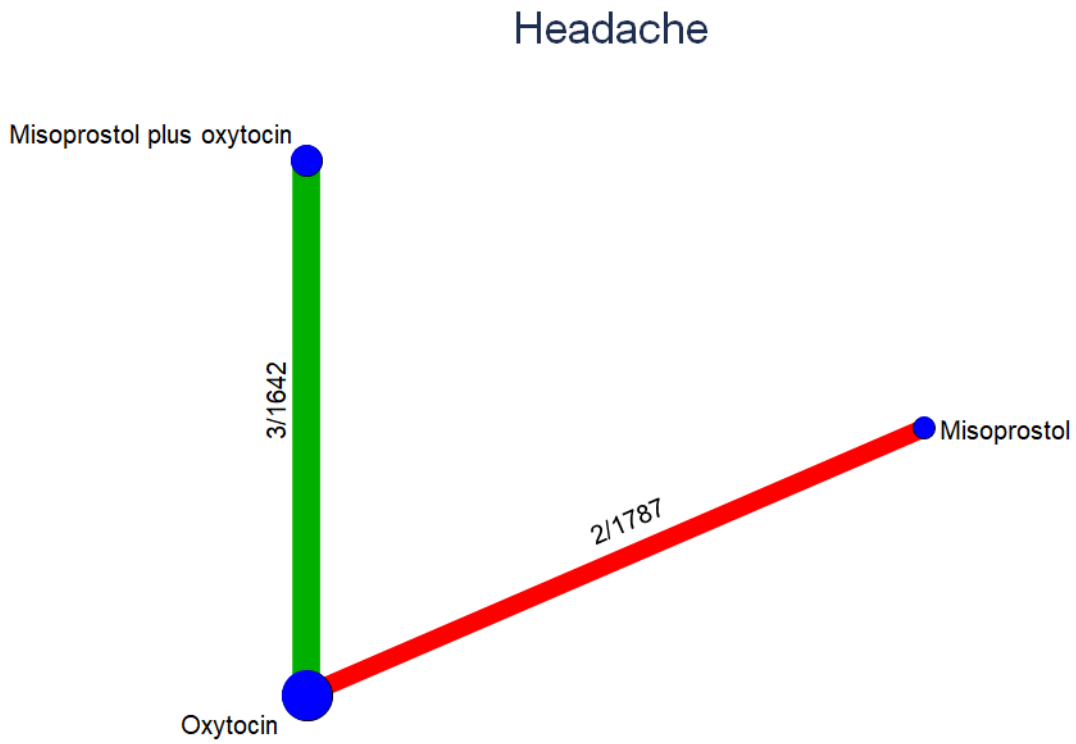
Side-effects: hypertension

Not reported.

Side-effects: headache

The network diagram for headache is presented in Figure 17.

Figure 17. Network Diagram for headache. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. 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 light green for moderate-certainty evidence and red for very low-certainty evidence.

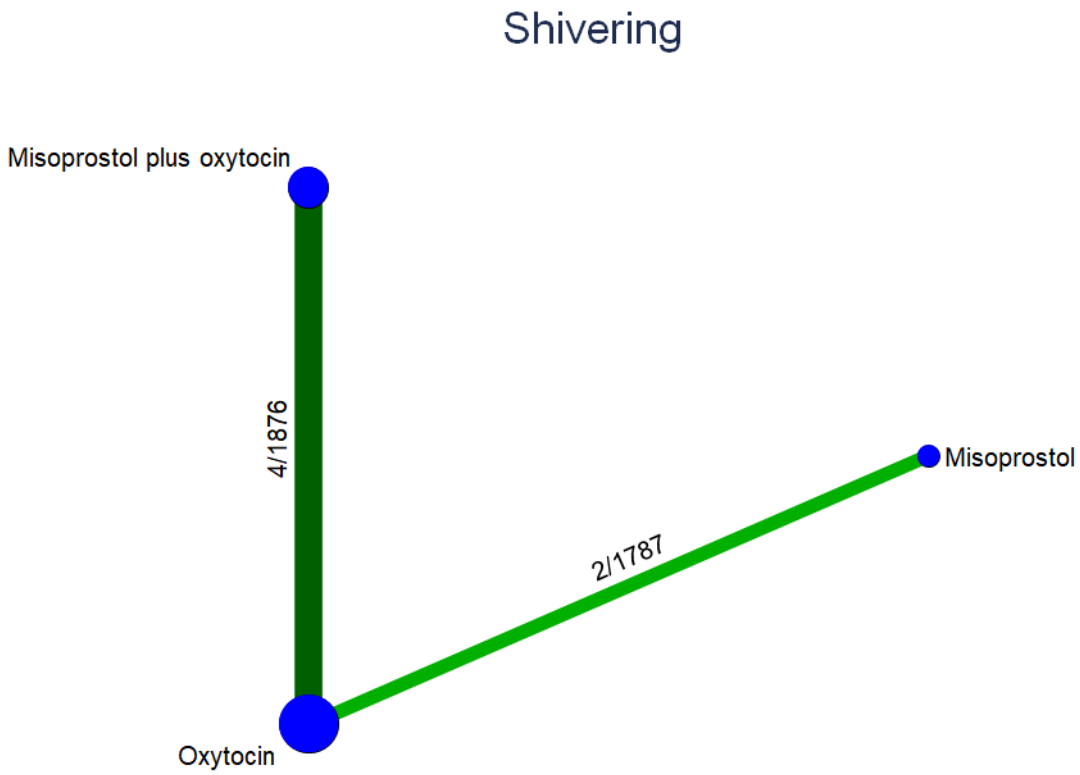


There were two available comparisons for this outcome; misoprostol was compared with oxytocin (2 trials, 1787 women) and misoprostol plus oxytocin was compared with oxytocin alone (3 trials, 1642 women). Based on the relative effects from pairwise meta-analysis, we cannot rule out important effects either way when misoprostol is given together with oxytocin compared with oxytocin given alone (RR 1.12, 95% CI 0.65 to 1.93, moderate-certainty evidence, Analysis 3.13). The evidence on misoprostol versus oxytocin was of very low-certainty evidence, and thus these effects remain unclear (Analysis 1.12).

Side-effects: shivering

Shivering is often dismissed as a trivial side-effect, but it may be very distressing for the mother when trying to bond with her baby and we have included in this outcome events reported as shivering following drug administration and also rigors. The network diagram for shivering is presented in Figure 18.

Figure 18. Network Diagram for shivering. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. 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 dark green for high-certainty evidence and light green for moderate-certainty evidence.



There were two available comparisons for this outcome; misoprostol was compared with oxytocin (2 trials, 1787 women) and misoprostol plus oxytocin was compared with oxytocin alone (4 trials, 1876 women). Based on the relative effects from pairwise meta-analysis, misoprostol probably results in a large increase in shivering compared with oxytocin (RR 2.70, 95% CI 2.28 to 3.19, moderate-certainty evidence, Analysis 1.13). Additionally, misoprostol plus oxytocin results in a large increase in shivering compared with oxytocin alone (RR 2.25, 95% CI 1.77 to 2.86, high-certainty evidence, Analysis 3.14).

Side-effects: tachycardia

Not reported.

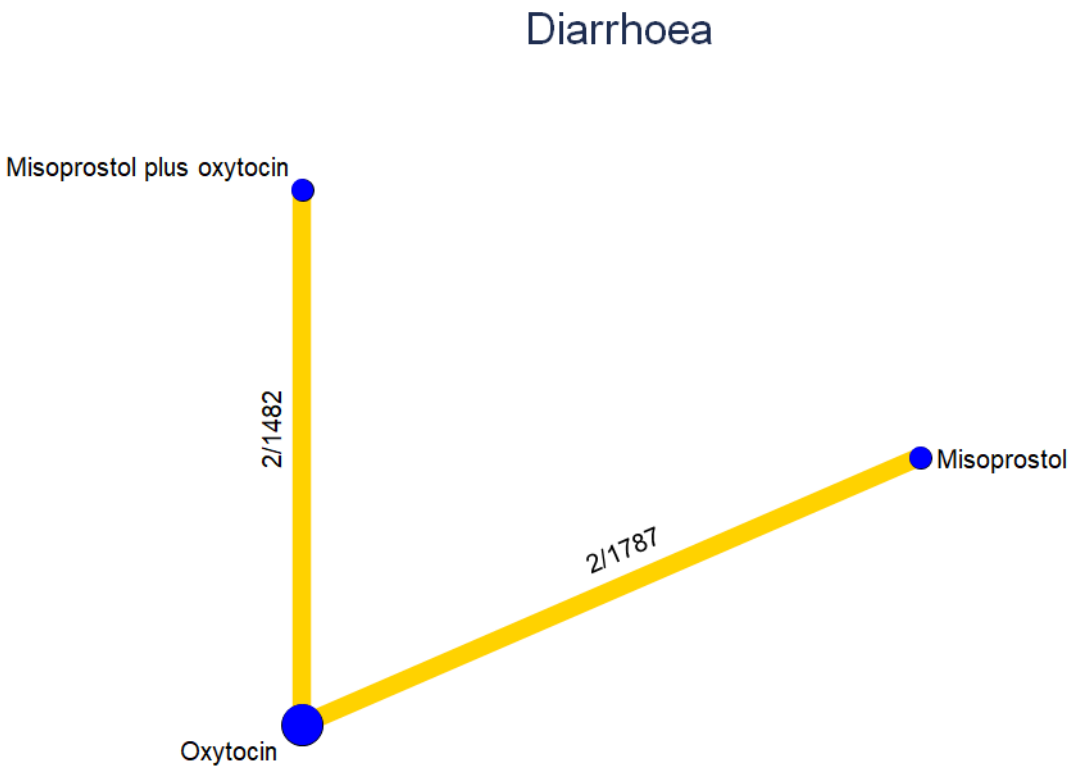
Side-effects: arrhythmia

Not reported.

Side-effects: diarrhoea

The network diagram for diarrhoea is presented in Figure 19.

Figure 19. Network Diagram for diarrhoea. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other. 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 orange for low-certainty evidence.



There were two available comparisons for this outcome; misoprostol was compared with oxytocin (2 trials, 1787 women) and misoprostol plus oxytocin was compared with oxytocin alone (2 trials, 1482 women). Based on the relative effects from pairwise meta-analysis, misoprostol is associated with a wide range of treatment effects when compared with oxytocin (RR 1.39, 95% CI 0.44 to 4.39, low-certainty evidence, Analysis 1.14). Although, two trials reported diarrhoea as an outcome for the comparison of misoprostol plus oxytocin versus oxytocin alone, only one trial reported events and contributed to the summary effect estimate. Based on the results from this single study, misoprostol plus oxytocin is also compatible with a wide range of treatment effects for this outcome compared with oxytocin alone (1 trial, 1421 women, RR 1.22, 95% CI 0.37 to 3.99, low-certainty evidence, Analysis 3.15).

Side-effects: abdominal pain

Not reported.

Participants reporting a sense of well-being

Not reported.

Participants reporting acceptability of the intervention

Not reported.

Participants reporting satisfaction with the intervention

Not reported.

Number of participants breastfeeding on discharge

Not reported.

DISCUSSION

Summary of main results

In summary, we reviewed seven trials, involving 3738 women in 10 countries. All trials were conducted in hospital settings and women

usually gave birth vaginally. The following agents were used in the included trials: oxytocin; misoprostol; misoprostol plus oxytocin; and Syntometrine® (oxytocin and ergometrine) plus oxytocin. Because of the limited number of trials, It was not possible to perform the planned network meta-analysis and rank the available uterotonic agents. We were able to summarise the effectiveness and side-effect evidence on three direct comparisons including misoprostol versus oxytocin, misoprostol versus Syntometrine® plus oxytocin infusion, and the misoprostol plus oxytocin combination versus oxytocin. We have performed only one indirect comparison between misoprostol plus oxytocin and misoprostol alone with the common comparator being oxytocin. An indirect comparison was also possible for Syntometrine® plus oxytocin versus oxytocin alone with the common anchor being misoprostol. We do not provide this comparison as the generated evidence would have been of very low certainty and thus non-informative.

We found moderate-certainty evidence that misoprostol, as first-line treatment uterotonic agent, probably increases the risk of requiring a blood transfusion compared with oxytocin. Low-certainty evidence suggests that misoprostol administration may increase the incidence of additional blood loss of 1000 mL or more. The comparison of misoprostol with oxytocin is compatible with a wide range of treatment effects for additional blood loss of 500 mL or more, the composite outcome of maternal mortality or severe morbidity, and the use of additional uterotonics. In terms of side-effects, misoprostol increases the risk for vomiting but is compatible with a wide range of treatment effects for fever compared with oxytocin.

The misoprostol plus oxytocin combination according to high-certainty evidence, makes little or no difference to the use of additional uterotonics and to blood transfusion compared with oxytocin alone. Moderate-certainty evidence suggests that for the misoprostol plus oxytocin combination we cannot rule out an important benefit for additional blood loss of 500 mL or more, nor important effects either way for additional blood loss of 1000 mL or more and the composite outcome of maternal mortality or severe morbidity. In terms of side-effects, the misoprostol plus oxytocin combination increases the incidence of fever and vomiting compared with oxytocin alone.

For all outcomes of interest, the available evidence on the misoprostol versus Syntometrine® plus oxytocin comparison was of very low certainty and these effects remain unclear.

From the indirect evidence, we found that the misoprostol plus oxytocin combination probably reduces the risk of blood transfusion and may reduce the risk of additional blood loss of 1000 mL or more compared with misoprostol alone. The combination makes little or no difference to vomiting. The data comparing misoprostol plus oxytocin combination against misoprostol alone are compatible with a wide range of treatment effects for the outcomes of additional blood loss of 500 mL or more, the composite outcome of maternal mortality or severe morbidity, the use of additional uterotonics, and fever.

Overall completeness and applicability of evidence

This review was set out to find the most effective uterotonic agent with the least side-effects for the first-line treatment of postpartum haemorrhage (PPH). Seven trials met the inclusion criteria and reported results for our primary and some of our secondary outcomes. No trials provided data on hypothermia, hypertension, arrhythmia, abdominal pain, maternal sense of well-being, acceptability of the intervention, maternal satisfaction, and breastfeeding outcomes. The majority of the trials recruited women experiencing PPH after a singleton term vaginal birth in low-resource hospital settings. Women with significant co-morbidities were largely excluded from all trials. The most frequent comparison was that of misoprostol plus oxytocin against oxytocin alone, with oxytocin being the standard of care. Misoprostol was compared with oxytocin and also against Syntometrine® combined with an oxytocin infusion. There were no studies involving injectable prostaglandins, ergometrine, or Syntometrine® as first-line treatments for primary PPH. Further trials are yet to report, which should allow for a more complete set of available comparisons in the future. See Characteristics of ongoing studies.

Quality of the evidence

Our confidence in the effect estimates of this review ranged from very low to high with the majority of the available evidence being of low certainty. Although, there is no single established approach for assessing the certainty of evidence generated by indirect comparisons, we applied the method proposed by the GRADE Working Group (Puhan 2014). See Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6; Summary of findings 7; Table 1. For this review, our aim was to include primarily trials where oxytocin was used already for prevention of PPH in line with current recommendations. For this reason, we decided to downgrade the certainty of the evidence for the comparison of misoprostol versus oxytocin where most weight to the summary effect estimate was provided by Winikoff 2010 (please see Analysis 1.7; Analysis 1.8; Analysis 1.12; Analysis 1.13). In this trial, the randomised study participants did not receive any uterotonic drug prophylaxis. This difference between the population included in this study and the population we were directly interested in has been considered as a source of indirectness in the review. Similarly, for the comparison of misoprostol plus oxytocin combination versus oxytocin alone we also decided to downgrade the certainty of evidence for indirectness when most weight to the summary effect estimate was provided by Hofmeyr 2004 (please see Analysis 3.3). That is because misoprostol was combined with oxytocin in this trial, but the timing of administration of misoprostol was not clear and we could not be confident that it was administered as first-line treatment for PPH to all women included in this study. For more information please see Characteristics of included studies.

Potential biases in the review process

Two review authors have been involved in two of the included trials, but did not participate in any decisions regarding these trials. For the purpose of this review, tasks, such as assessment for inclusion or exclusion, trial quality, and data extraction were carried out by other members of the team who were not directly involved in these two trials.

Significant heterogeneity was observed in two of the analyses comparing misoprostol against oxytocin (Analysis 1.1; Analysis 1.4;). For this comparison, there were two included studies that had differences in the management of third stage of labour. Specifically, one trial used oxytocin for prevention of PPH and one did not use any prophylaxis (see Characteristics of included studies). We planned to investigate such heterogeneity by carrying out a number

of pre-specified subgroup analyses including a subgroup analysis according 'uterotonic administration prior to enrolment'. However, we decided not to formally investigate the heterogeneity in these analyses by carrying out the planned subgroup analyses because only two trials contributed data and a subgroup analysis would not provide robust evidence of effect modification. Both studies had a similar direction of effect with only the size of the effect varying. The magnitude of the difference was not considered to be practically important, which means that it will not result in different recommendations for the different subgroups. Lastly, this subgroup analysis would have focused on a relationship between studies and not within studies, which would have further limited the confidence in such analysis.

Agreements and disagreements with other studies or reviews

Our results are consistent with an existing Cochrane Review (Mousa 2014).

AUTHORS' CONCLUSIONS

Implications for practice

The current World Health Organization (WHO) recommendation states that intravenous oxytocin alone is the recommended uterotonic agent for the treatment of postpartum haemorrhage (PPH) (WHO 2012). The available evidence suggests that oxytocin used as first-line treatment of PPH probably is more effective than misoprostol with less side-effects. As a result, the balance of effects is expected to favour oxytocin. Adding misoprostol to the conventional treatment of oxytocin probably makes little or no difference to effectiveness outcomes, and is also associated with more side-effects.

The absence of evidence for the injectable prostaglandins, ergometrine, or Syntometrine® as first-line treatment for PPH has implications to practice. As the effects for these uterotonic agents are yet to be determined, providers need to be aware of the lack of evidence and apply caution to their use as first-line treatments for PPH.

Implications for research

We identified that many outcomes that are considered core outcomes (Meher 2019) and should be reported in trials evaluating uterotonic agents for the treatment of PPH, are rarely investigated. Specifically, women's well-being and views regarding the agents used, severe maternal morbidity such as shock, and breastfeeding at discharge were not reported in any of trials included in the review. Although side-effects of each uterotonic agent were also identified as core outcomes, these were often not reported.

Based on the available evidence, the current WHO recommendation for intravenous oxytocin as first-line treatment of PPH is justified. Most of the evidence comes from low-resource countries where there is a disproportionate burden from PPH. However, oxytocin needs to be kept refrigerated (2 °C to 8 °C) to maintain its potency. Storage at room temperature and temperature variations during the shipment of oxytocin from the manufacturer to the healthcare providers, following the routine supply chain, affects the potency of oxytocin (Hogerzeil 1993;WHO 1993). Carbetocin is a heat-stable analogue of oxytocin with agonist properties. Because it is heat-stable it can overcome the difficulties with maintaining a cold chain from the manufacturer to the healthcare providers. The heat-stable carbetocin is now recommended for prevention of PPH and has been evaluated against oxytocin for the prevention of PPH in a large randomised trial (Widmer 2018). Research is required to determine the effects of carbetocin as a first-line treatment of PPH, especially in low-resource settings.

In summary, there is considerable uncertainty over which is the best uterotonic agent to use for the first-line treatment of PPH. There is lack of evidence on the effectiveness of commonly used drugs, such as injectable prostaglandins (i.e. carboprost and sulprostone), ergometrine, and Syntometrine®. The available evidence for most of the other uterotonic agents is generally of low certainty. Therefore, further research should be conducted to determine the effectiveness and side-effects of the available uterotonics as first-line treatment for PPH, and new evidence-based guidelines should be shaped to ensure a positive childbirth experience.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Blum 2010

Study characteristics	
Methods	2-arm active-controlled double-dummy randomised controlled trial
Participants	809 women were randomised in a hospital setting in Burkina Faso, Egypt, Turkey and Vietnam between August, 2005, and January, 2008. The population comprised women giving birth vaginally, at mixed risk for PPH. They had received prophylactic oxytocin intravenously or intramuscularly during the third stage of labour and were diagnosed with PPH due to suspected uterine atony, either by clinical judgement or blood loss reaching 700 mL in the calibrated drape during the first hour after delivery. Women were not eligible for the trial if their PPH was suspected to have another cause other than uterine atony, oxytocin was not received during the third stage of labour or if they underwent a caesarean section.
Interventions	Misoprostol 800 mcg (4 tablets of 200 mcg) administered sublingually versus oxytocin 40 IU administered by an intravenous infusion.
Outcomes	The study recorded the following outcomes: additional blood loss of more than 500 mL; composite of maternal death or severe morbidity; death; additional uterotonics; additional blood loss of more than 1000 mL; additional surgical procedures, blood transfusion or other blood products; mean additional blood loss; fever; nausea; vomiting; headache; shivering; diarrhoea.
Notes	Contact with study authors for additional information: no. Additional data from authors: no.
Risk of bias	

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

Blum 2010 *(Continued)*

Random sequence generation (selection bias)	Low risk	A computer-generated random allocation sequence in blocks of 10 was derived by Gynuity Health Projects, New York, NY, USA, and was not revealed until data collection and cleaning were completed.
Allocation concealment (selection bias)	Low risk	Sealed and numbered opaque boxes contained the treatment allocation and were opened in strict numeric sequence.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both providers and women were blinded to treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
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 (NCT00116350).
Method to measure blood loss for all outcomes	Low risk	Investigators appraised blood loss by a polyurethane receptacle with calibrated funnel (Brass-V Drapes, Excellent Fixable Drapes, Madurai, Tamil Nadu, India), placed under the woman's buttocks after delivery of the baby.
Funding and conflicts of interest	Low risk	This research was funded by the Bill & Melinda Gates Foundation and no conflicts of interest were identified.

Hofmeyr 2004

Study characteristics	
Methods	2-arm active-controlled double-blind randomised trial
Participants	244 women were randomised in a hospital setting in South Africa between January, 2002, and December, 2003. The population comprised women giving birth vaginally, at mixed risk for PPH. They received prophylactic oxytocin 10 IU or Syntometrine® 1 ampoule without specifying the route of administration during the third stage of labour. The women included in the trial were bleeding more than expected at least 10 minutes after giving birth due to uterine atony, and additional uterotonic therapy was required. Exclusion criteria were not specified.
Interventions	Misoprostol 1000 mcg administered through multiple routes (1 tablet of 200 mcg orally, 2 tablets of 200 mcg sublingually, and 2 tablets of 200 mcg rectally) plus oxytocin administered through an intravenous infusion (some women received ergometrine plus oxytocin).
Outcomes	The study recorded the following outcomes: additional blood loss of more than 500 mL; composite of maternal death or severe morbidity; death; additional uterotonics; additional blood loss of more than 1000 mL; additional surgical procedures; blood transfusion or other blood products; mean additional blood loss; fever (≥ 38.5^{0}C); shivering.
Notes	Contact with study authors for additional information: yes. Additional data from authors: no.
Risk of bias	

Hofmeyr 2004 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated random sequence was used.
Allocation concealment (selection bias)	Low risk	Treatment packs were prepared independently and numbered consecutively. The treatment sequence was kept sealed and the code was broken only after complete entry and checking of all trial data.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study participants and care givers were blinded to treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Although 244 women were enrolled in the trial, the pack numbers on the data sheets were incomplete for 6 women. The group allocation of these women was therefore unknown and they could not be included in the analysis. More missing data per outcome, but not exceeding 10%.
Selective reporting (reporting bias)	Unclear risk	The study report matches the study protocol that was registered retrospectively (ISRCTN72263357).
Method to measure blood loss for all outcomes	Low risk	A low-profile plastic 'fracture bedpan' was placed under women's buttocks. Any small swabs soaked in blood were dropped into the bedpan. After 1 hour, the blood collected in the bedpan was measured in a graduated measuring jug.
Funding and conflicts of interest	Low risk	This research was funded by the University of the Witwatersrand (South Africa) and no conflicts of interest were identified.

Lokugamage 2001

Study characteristics	
Methods	2-arm active-controlled double-dummy randomised trial
Participants	64 women were randomised in a hospital setting in South Africa. The population comprised women giving birth either vaginally or by caesarean section, at mixed risk for PPH. It was not specified if a uterotonic was given in the third stage for prevention of PPH. The women included in the trial had an estimated blood loss greater than 500 mL with visible signs of continued heavy vaginal bleeding and whose uterus was poorly contracted within 24 hours of birth. Women were not eligible for the trial if they were hypertensive at the time of potential recruitment, had cardiac abnormalities, ongoing severe asthma, connective tissue disorders, any contra-indications to prostaglandin therapy or haemorrhage due to obvious genital tract trauma.
Interventions	Misoprostol 800 mcg (4 tablets of 200 mcg) administered rectally versus Syntometrine® (ergometrine 500 mcg plus oxytocin 5 IU) administered intramuscularly plus oxytocin 10 IU administered by an intravenous infusion.
Outcomes	The study recorded the following outcomes: composite of maternal death or severe morbidity; additional uterotonics; additional surgical procedures.

Lokugamage 2001 *(Continued)*

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 by generating random numbers via STATA, a statistical software package.
Allocation concealment (selection bias)	Low risk	The randomly selected group allocations were placed in sealed sequentially-numbered envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Obstetricians were aware of the study allocation but not midwifes. It is unclear if this was an effective method of blinding for the care-giving team. It is also unclear if study participants were blinded, but it can be assumed they were blinded, in view of the use of a double-dummy in the trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Midwives mainly measured the bleeding and assessed uterine contraction, and were blinded to treatment allocations.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 patient was recruited to the misoprostol arm, but was excluded from the analysis because the haemorrhage was due to uterine rupture.
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification. For some of the outcomes only the 'P' values of statistical significance were reported.
Method to measure blood loss for all outcomes	High risk	Investigators appraised blood loss by visual estimation of attending physicians.
Funding and conflicts of interest	Low risk	This study was funded by the University College London and the University of Natal. No conflicts of interest were identified.

Walraven 2004

Study characteristics

Methods	2-arm active-controlled randomised trial
Participants	160 women were randomised in a hospital setting in Gambia between November, 2002, and October, 2003. The population comprised women giving birth vaginally, at mixed risk for PPH, who had received prophylactic oxytocin 10 IU or Syntometrine ® 1 ampoule without specifying the route of administration during the third stage of labour. The women included in the trial had blood loss greater than 500 mL within the first hour postpartum, due to suspected uterine atony. Women were not eligible for the trial if they had a caesarean section, their blood loss was less than 500 mL in the first hour after delivery, the delivery occurred at less than 28 weeks of gestation, inadequate uterine contraction was not thought to be a possible causative factor for the PPH or if they were not consenting.
Interventions	Misoprostol 600 mcg administered through multiple routes (1 tablet of 200 mcg orally, and 2 tablets of 200 mcg sublingually) plus oxytocin (trialists defined as oxytocics with no further details).
Outcomes	The study recorded the following outcomes: additional blood loss of more than 500 mL; composite of maternal death or severe morbidity; death; additional uterotonics; additional blood loss of more than

Walraven 2004 *(Continued)*

	1000 mL; additional surgical procedures; blood transfusion or other blood products; mean additional blood loss; fever; nausea; headache; 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	Method of sequence generation was not reported.
Allocation concealment (selection bias)	Low risk	They were enrolled by opening the next in a series of randomised treatment packs in opaque envelopes containing either misoprostol or placebo tablets.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The tablets were similar in size and colour but not in shape. Efforts to obtain identical placebo tablets were unsuccessful.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The randomisation code was broken only after entry and checking of data.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no withdrawals after enrolment, and all outcomes were analysed according to the allocated study group.
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was unavailable for verification.
Method to measure blood loss for all outcomes	Low risk	The blood collected in the bedpan was then transferred to a measuring jar. The measuring jar and all gauzes and pads used were put in a standard plastic bag and the total difference between the dry and wet weights was calculated.
Funding and conflicts of interest	Unclear risk	Funding sources were not reported. No other conflicts of interest were identified.

Widmer 2010

Study characteristics

Methods	2-arm active-controlled double-blind randomised trial
Participants	1422 women were randomised in a hospital setting in Argentina, Egypt, South Africa, Thailand, and Vietnam between July, 2005, and August, 2008. The population comprised women giving birth vaginally, at mixed risk of PPH, who had received prophylactic oxytocin 10 IU or ergometrine or prostaglandins without specifying the dose or route of administration during the third stage of labour. The women included in the trial had clinically diagnosed PPH that was suspected to be due to uterine atony, and needed additional uterotonics. Women were not eligible for the trial if: delivery was by caesarean section; misoprostol could not be given sublingually; any severe allergic or bleeding disorders (e.g. haemophilia) were recorded; temperature was higher than 38.5°C; the delivery was defined as a miscarriage according to local gestational age limits; or the placenta was not delivered.
Interventions	Misoprostol 600 mcg (3 tablets of 200 mcg) administered sublingually plus conventional uterotonics versus oxytocin 10 IU administered intramuscularly or by a slow intravenous injection.

Widmer 2010 *(Continued)*

Outcomes	The study recorded the following outcomes: additional blood loss of more than 500 mL; composite of maternal death or severe morbidity; death; additional uterotonics; additional blood loss of more than 1000 mL; blood transfusion or other blood products; mean additional blood loss; fever; nausea; vomiting; headache; shivering; diarrhoea.
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 computer-generated randomisation sequence was derived centrally by Gynuity Health Projects, New York, NY, USA, stratified by country with varying blocks of 6 and 8.
Allocation concealment (selection bias)	Low risk	To conceal allocation, treatment boxes were sealed and numbered sequentially according to the randomisation sequence, and distributed in the order that women were judged to be eligible and were enrolled in the study.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment boxes were identical in appearance for both groups, and placebo tablets were identical in shape, colour, weight, feel, and taste to misoprostol tablets. Both providers and participants were masked to treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 women were lost to follow-up (blood loss not recorded) and 3 did not receive the intervention.
Selective reporting (reporting bias)	Unclear risk	The study report matches the study protocol that was registered retrospectively (ISRCTN34455240).
Method to measure blood loss for all outcomes	Low risk	Blood collection started immediately after the study drug was given. A fresh, non-absorbent sheet was placed under the buttocks of the woman. A low-profile plastic fracture bedpan was positioned below the woman's perineum to collect all subsequent blood lost for 90 minutes. The blood in the bedpan plus any spilled blood from the non-absorbent sheet or blood-soaked gauze swabs, or both, was transferred to a jar and the volume was measured. At the centre in Egypt, blood was collected into a calibrated plastic sheet that was placed below the woman immediately after she took the study drug, and the volume was measured accordingly. Measures of blood loss were recorded at 60 minutes and 90 minutes after randomisation.
Funding and conflicts of interest	Low risk	This research was funded by the Bill & Melinda Gates Foundation through a grant to Family Care International and Gynuity Health Projects. Additional funds were provided by the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction. No conflicts of interest were identified.

Winikoff 2010

Study characteristics

Winikoff 2010 *(Continued)*

Methods	2-arm active-controlled double-dummy randomised trial
Participants	978 women were randomised in a hospital setting in Ecuador, Egypt and Vietnam between August, 2005, and January, 2008. The population comprised women giving birth vaginally, at mixed risk for PPH, who were not exposed to prophylactic oxytocin during third stage of labour. The women included in the trial had blood loss that exceeded 700 mL due to suspected uterine atony. Women were not eligible for the trial if they had a known allergy to prostaglandins, received any uterotonic agent in labour, underwent caesarean section, delivered outside the study site or their postpartum bleeding was not suspected to be due to atonic uterus.
Interventions	Misoprostol 800 mcg (4 tablets of 200 mcg) administered sublingually versus oxytocin 40 IU administered by an intravenous infusion.
Outcomes	The study recorded the following outcomes: additional blood loss of more than 500 mL; composite of maternal death or severe morbidity; death; additional uterotonics; additional blood loss of more than 1000 mL; additional surgical procedures; blood transfusion or other blood products; mean additional blood loss; fever; nausea; vomiting; headache; shivering; diarrhoea.
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 allocation sequence in blocks of ten was maintained by Gynuity Health Projects, New York, NY, USA.
Allocation concealment (selection bias)	Low risk	The random allocation sequence was concealed from study staff who enrolled and allocated treatments. Study staff immediately administered the next sequentially numbered allocated treatment packet, which contained 1 active treatment and matching placebo.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Providers and women were blinded to treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
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 (NCT00116350).
Method to measure blood loss for all outcomes	Low risk	Immediately after delivery the blood collection drape was placed beneath the woman's buttocks. Study staff measured postpartum blood loss by use of a polyurethane receptacle with a calibrated funnel.
Funding and conflicts of interest	Low risk	This research was funded by the Bill & Melinda Gates Foundation and no conflicts of interest were identified.

Zuberi 2008

Study characteristics	
Methods	2-arm active-controlled double-blind randomised trial
Participants	61 women were randomised in a hospital setting in Pakistan between December, 2005, and April, 2007. The population comprised women giving birth vaginally, at mixed risk for PPH. They received prophylactic oxytocin 10 IU by an intravenous bolus or oxytocin 5 IU plus ergometrine 400 mcg administered intramuscularly or intravenously during the third stage of labour. The women included in the trial received the standard additional injectable oxytocics for treatment of PPH, due to suspected uterine atony and blood loss exceeding 500 mL. Women were not eligible for the trial if they underwent caesarean section, their gestational age was less than 28 weeks at time of delivery, they were not consenting or if their blood loss was less than 500 mL.
Interventions	Misoprostol 600 mcg (3 tablets of 200 mcg) administered sublingually plus oxytocin administered intravenously versus oxytocin administered intravenously alone.
Outcomes	The study recorded the following outcomes: additional blood loss of more than 500 mL; composite of maternal death severe morbidity; death; additional uterotonics; additional blood loss of more than 1000 mL; additional surgical procedures; blood transfusion or other blood products; mean additional blood loss; change in haemoglobin measurements before and after birth; fever; nausea; vomiting; headache; shivering; diarrhoea.
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 sample was randomised in blocks of 10, stratified by site, using a computer-generated random sequence provided by Gynuity Health Projects, New York, NY, USA, where the code was kept.
Allocation concealment (selection bias)	Low risk	A member of study team gave each woman the pills in the next randomised study envelope. The randomisation code was concealed until all data were entered and cleaned.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All women, providers and investigators were blinded to the treatment assignments.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 women in the misoprostol arm were excluded from the analysis of measured postpartum blood loss, because of incomplete measurements.
Selective reporting (reporting bias)	Low risk	The study report matches the study protocol that was registered prospectively (NCT00116480).
Method to measure blood loss for all outcomes	Low risk	The blood collected on the bedpan and perineal pan was transferred to a calibrated jug for measurement. All used gauzes and pads were counted and placed in a plastic bag which was then weighed.

Zuberi 2008 *(Continued)*

Funding and conflicts of interest	Low risk	This research was funded by the Bill & Melinda Gates Foundation through a grant to Gynuity Health Projects and Family Care International. The Foundation had no role in the actual planning, writing or submission of this paper.

IU: international unit; mcg: microgram; PPH: postpartum haemorrhage

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

Study	Reason for exclusion
Abbas 2019	Not eligible intervention.
Chatterjee 2016	Not eligible study design.
IRCT2012122411862N1	Not eligible intervention.
Raghavan 2016	Not eligible study design.
Sahhaf 2014	Not eligible intervention.
Suhrabi 2016	Not eligible intervention.
Takagi 1976	Not eligible study design.

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

Maged 2016

Methods	2-arm active-controlled double-blind randomised trial
Participants	100 women were randomised in a hospital setting in Egypt between May, 2013, and December, 2014. The population comprised women giving birth vaginally, at mixed risk for PPH. It was not specified if a uterotonic was given in the third stage for prevention of PPH. The women included in the trial had vaginal bleeding greater than 500 mL after birth and uterine atony confirmed by abdominal palpation. Women were not eligible for the trial if their gestational age was less than 37 weeks; they had genital tract trauma; coagulation defects; hypertension; preeclampsia; cardiac, renal, or liver diseases; epilepsy or known hypersensitivity to carbetocin or oxytocin.
Interventions	Carbetocin 100 mcg administered by an intravenous bolus versus oxytocin 5 IU administered by an intravenous bolus.
Outcomes	The study recorded the following outcomes: composite of maternal death or severe morbidity; death; additional uterotonics; additional blood loss of 1000 mL or more after recruitment to cessation of active bleeding; additional surgical procedures; blood transfusion or other blood products; mean additional blood loss; change in haemoglobin measurements before and after birth; nausea; vomiting; headache; shivering; tachycardia.
Notes	Queries relating to study data were identified through our screening for scientific integrity/trustworthiness. We contacted the trial author on (July 2020) but have not yet received a response. Contact email: prof.ahmedmaged@gmail.com

NCT01116050	
Methods	Randomised controlled trial.
Participants	Not recorded.
Interventions	Misoprostol 1000 mcg administered rectally versus placebo
Outcomes	The study recorded the following outcomes: additional blood loss of more than 500 mL after recruitment to cessation of active bleeding; composite of death or severe morbidity; additional uterotonics; additional blood loss of more than 1000 mL after recruitment to cessation of active bleeding.
Notes	Awaiting full-text publication.

IU: international unit; **mcg:** microgram; **mL:** millilitre; **PPH:** postpartum haemorrhage

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

ISRCTN16416766	
Study name	COPE. Carboprost vs oxytocin as the first line treatment of primary postpartum haemorrhage; a phase IV, double-blind, double-dummy, randomised controlled trial.
Methods	Double-blind, double-dummy, randomised controlled trial.
Participants	Inclusion criteria: women aged 16 years or older with a requirement for medical treatment of primary PPH. Exclusion criteria: women who have hypersensitivity to carboprost or oxytocin, have known cardiac or pulmonary disease, have previously been treated as part of the trial, have already received a treatment uterotonic drug or have a stillbirth, have opted out of participation.
Interventions	Carboprost 250 mcg administered intramuscularly plus placebo 1 mL administered intravenously versus oxytocin 10 IU administered intravenously plus placebo 1 mL administered intramuscularly.
Outcomes	Primary outcome measure Blood transfusion - any RBC blood transfusion or cell salvage of ≥ 300 mL commenced any time between randomisation and 48 hours after randomisation (or hospital discharge if earlier than 48 hours), measured using medical notes. Secondary outcome measures 1. Volume of blood transfusion from randomisation up to 48 hours (or hospital discharge if earlier), measured using medical notes. 2. Use of a further uterotonic drug from randomisation up to 24 hours after randomisation, measured using medical notes. 3. Composite outcome of any organ dysfunction based on WHO near-miss approach for maternal health (2) from randomisation up to hospital discharge (or 4 weeks whichever is earlier). 4. Hysterectomy from randomisation up to hospital discharge (or 4 weeks whichever is earlier), measured using medical notes. 5. Blood loss in mL commencing in the first 24 hours from randomisation, up to cessation of active bleeding, measured using medical notes. 6. Blood loss ≥ 1000 mL, measured using medical notes. 7. Haemoglobin closest to 24 hours after randomisation, measured using medical notes. 8. Shock within 24 hours of randomisation, measured using medical notes. 9. Maternal death within 4 weeks of the birth where PPH was a contributing factor (it does not need to be the primary cause), measured using medical notes. 10. Non-pharmacological approach to treat or investigate bleeding from randomisation up to hospital discharge, measured using medical notes. 11. Manual removal of placenta post-randomisation up to hospital discharge, measured using medical notes.

ISRCTN16416766 *(Continued)*

	12. Any adverse reactions of the intervention for the mother (i.e. hypotension occurring within 2 minutes of Investigational Medicinal Product (IMP) administration, and all other adverse reactions occurring within 2 hours of administration), measured using medical notes. 13. 'Skin-to-skin' care with baby within the first hour after birth, measured using medical notes. 14. Separation from new-born in first hour after birth, measured using medical notes. 15. Breastfeeding, measured at 24 hours, 48 hours (or hospital discharge if sooner) and 4 weeks. 16. Woman's experience, measured using Childbirth Experience Questionnaire (CEQ) at 4 weeks. 17. Resource use, measured using EQ-5D-5L, resource use questionnaire and hospital episode statistics at 24 hours and 4 weeks.
Starting date	September 2018
Contact information	Mr Alex Astor Address Research Support Office 2nd Floor Block D Waterhouse Building 3 Brownlow Street Liverpool L69 3GL United Kingdom +44 (0)1517948739 sponsor@liverpool.ac.uk
Notes	Study team not contacted.

NCT01485562

Study name	Treatment of postpartum haemorrhage (PPH) using misoprostol in home births.
Methods	A double-blind individually-randomised controlled study of misoprostol versus placebo for treatment in home births in the Chitral district, in the Khyber Pakhtunkhwa province in Pakistan. The purpose of the study is to assess the overall clinical and programmatic effectiveness of Traditional Birth Attendants (TBAs) administering 800 mcg sublingual misoprostol to treat PPH at the community level.
Participants	Inclusion criteria: pregnant women who deliver at home.
Interventions	Misoprostol 800 mcg (4 tablets of 200 mcg) administered sublingually versus placebo (4 tablets) administered sublingually.
Outcomes	Primary outcome: haemoglobin concentration of greater than or equal to 2 g/dL from pre- to post-delivery. Secondary outcomes: number of participants who experience side-effects; number of women who experience side-effects and the severity of side-effects, as rated on a scale; additional care provided; number of women who received additional interventions; number of women who received care by a skilled provider, and the type of care provided; number of women who found misoprostol treatment to be acceptable, as rated on a scale; number of women who experience severe adverse events, defined as uterine rupture, hysterectomy, hospitalisation, maternal deaths, and neonatal deaths.
Starting date	May 2012
Contact information	Zafar Khan Aga Khan Health Services
Notes	Study team contacted for results with no response.

NCT01508429

Study name	Misoprostol for the treatment of postpartum haemorrhage (PPH) following self-administration of misoprostol prophylaxis in home deliveries
Methods	A double-blind individually-randomised controlled study.
Participants	Inclusion criteria: pregnant women who are likely to deliver at home.
Interventions	Standard of care plus 800 mcg misoprostol (4 tablets of 200 mcg) versus standard of care plus placebo (4 tablets).
Outcomes	Primary outcome: haemoglobin of greater than or equal to 2 g/dL from pre- to post-delivery. Secondary outcomes: side-effects, including perceived severity, and additional care provided; any serious adverse outcomes, including uterine rupture, hysterectomy, hospitalisation, maternal deaths, and neonatal deaths; additional interventions, including additional interventions and additional care provided to the woman, referrals, and transfers; acceptability and management of side-effects, and acceptability of interventions.
Starting date	July 2012
Contact information	Shafiq Mirzazada, Aga Khan Services
Notes	Study team contacted for results with no response.

NCT01600612

Study name	Oxytocin, carbetocin and misoprostol for treatment of postpartum haemorrhage: a multicentric randomised trial
Methods	A multicentric randomised trial.
Participants	Inclusion criteria: women with atonic PPH who delivered vaginally. Exclusion criteria: women who deliver by caesarean section, with retained placenta, with traumatic PPH, associated coagulopathy, and those who refuse to participate in the study.
Interventions	Oxytocin 30 IU administered intravenously versus misoprostol 600 mcg administered sublingually versus carbetocin 100 mcg administered intravenously.
Outcomes	Primary outcome: cessation of bleeding. Secondary outcomes: time needed to control bleeding (minutes); amount of blood loss till control of bleeding (mL), changes in haemoglobin levels (g) before and after treatment; changes in haematocrit values (%) before and after treatment; use of additional uterotonics; the rate of complications (%); the necessity for surgical intervention; and the cost of each medication.
Starting date	September 2012
Contact information	Salah M Rasheed. Sohag University Egypt.
Notes	Study team contacted for results with no response.

NCT01619072

Study name	A randomised controlled community study of the effectiveness of misoprostol for PPH treatment at the community level (home births attended by Primary Care Unit staff) in Etay El Barood and Kafr El Dawar Districts (El Beheira Governorate), Egypt
Methods	Randomised controlled community-based trial.
Participants	Inclusion criteria: women having a vaginal delivery and willing and able to give informed consent aged 18-45 years. Exclusion criteria: women too advanced in active labour, allergic to misoprostol, having hypertensive disorders, with multiple gestation, previous caesarean section, suspected stillbirth, antepartum haemorrhage, and previous complications in the third trimester.
Interventions	Standard of care plus misoprostol 800 mcg administered sublingually or standard of care plus placebo.
Outcomes	Primary outcome: change in haemoglobin measurement of > 2 g/dL pre- to post-delivery.
Starting date	November 2012
Contact information	Mohamed Cherine Ramadan. El Galaa Teaching Hospital.
Notes	Study team contacted for results with no response.

NCT02306733

Study name	Ergometrine versus oxytocin in the management of atonic post-partum haemorrhage (PPH) in women delivered vaginally: a randomised controlled trial.
Methods	Randomised controlled trial.
Participants	Inclusion criteria: women experiencing PPH, due to uterine atony, signing informed consents. Exclusion criteria: gestational age < 37 weeks, hypertension, cardiac disease or pre-eclampsia.
Interventions	Ergometrine 400 mcg administered intravenously versus oxytocin 10 IU (Syntocinon® Novartis, Switzerland) administered intravenously.
Outcomes	Primary outcome: the need for additional uterotonics. Secondary outcome: the development of major PPH.
Starting date	November 2014
Contact information	AbdelGany MA Hassan, Cairo University Hospitals, Egypt.
Notes	Study team contacted for results, write up and data analysis is ongoing.

NCT02410759

Study name	Carbetocin versus oxytocin in the management of atonic post partum haemorrhage (PPH) in women delivered vaginally: a randomised controlled trial.

NCT02410759 *(Continued)*

Methods	Randomised controlled trial.
Participants	Inclusion criteria: women aged 20 to 40 years with atonic PPH who delivered vaginally. Exclusion criteria: women with preterm delivery, hypertension, pre-eclampsia, cardiac, renal, liver diease, epilepsy and known hypersensitivity to carbetocin.
Interventions	Carbetocin 100 mcg administered intramuscularly or ergometrine 500 mcg administered intramuscularly.
Outcomes	Primary outcome: the need for additional uterotonics. Secondary outcome: the development of major PPH.
Starting date	April 2015
Contact information	AbdelGany MA Hassan, Cairo University Hospitals, Egypt.
Notes	Study team contacted for results, write up and data analysis is ongoing.

NCT03584854

Study name	Second-line uterotonics in postpartum hemorrhage: a randomized clinical trial
Methods	Randomised controlled trial.
Participants	Inclusion criteria: women aged 18 to 50 years with atonic PPH who delivered by non-emergent caesarean section. Exclusion criteria: women delivering at < 24 weeks, any hypertensive disorders, cardiac diease, asthma, refusal of transfused blood products, coagulation disorders, known hypersensitivity to ergometrine or carboprost.
Interventions	Carboprost 250 mcg administered intramuscularly (followed by ergometrine if needed) or ergometrine 200 mcg administered intramuscularly (followed by carboprost if needed).
Outcomes	Primary outcome: uterine tone at 10 minutes after drug administration Secondary outcomes: uterine tone at 5 minutes after drug administration, need for additional uterotonics, need for blood transfusion, additional surgical or radiological interventions to control the bleeding, amount of blood loss, change in haematocrit, length of hospital stay, maternal morbidity related to PPH (e.g. cardiovascular event, intubation, ICU admission, hypovolaemic shock, adverse study drug reaction).
Starting date	March 2019
Contact information	Naida M Cole, MD, Brigham and Women's Hospital, 75 Francis Street, Boston MA 02115
Notes	Active not recruiting

NCT03870503

Study name	Carbetocin versus oxytocin plus sublingual misoprostol in the management of atonic post-partum hemorrhage (PPH) after vaginal delivery: a randomized controlled trial

NCT03870503 *(Continued)*

Methods	Randomised controlled trial.
Participants	Inclusion criteria: women aged 20 to 40 years with atonic PPH who delivered vaginally. Exclusion criteria: women with preterm delivery, hypertension, pre-eclampsia, cardiac, renal, liver diease, epilepsy and known hypersensitivity to carbetocin or oxytocin.
Interventions	Oxytocin 20 IU administered by an intravenous infusion or oxytocin 20 IU administered by an intravenous infusion plus misoprostol 400 mcg administered sublingually or carbetocin 100 mcg administered by an intravenous bolus injection.
Outcomes	Primary outcome: the amount of blood loss. Secondary outcome: the development of major PPH, the need for blood transfusion.
Starting date	April 2019
Contact information	Hany F Allam, MD, Aswan University Hospital, Aswan, Egypt, 81528
Notes	Recruting

ICU: intensive care unit; **IU:** international unit; **mcg:** microgram; **mL:** millilitre; **PPH:** postpartum haemorrhage**RBC:** red blood cell

DATA AND ANALYSES

Comparison 1. Misoprostol versus oxytocin

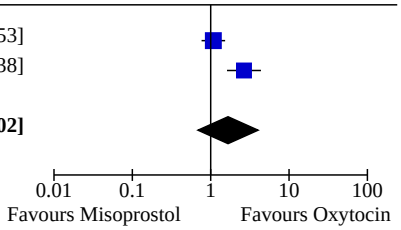
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Additional blood loss of 500 mL or more	2	1787	Risk Ratio (IV, Random, 95% CI)	1.66 [0.69, 4.02]
1.2 Composite of maternal death or severe morbidity	2	1787	Risk Ratio (IV, Random, 95% CI)	1.98 [0.36, 10.72]
1.3 Death	2	1787	Risk Ratio (IV, Random, 95% CI)	0.99 [0.06, 15.74]
1.4 Additional uterotonics	2	1787	Risk Ratio (IV, Random, 95% CI)	1.30 [0.57, 2.94]
1.5 Additional blood loss of 1000 mL or more	2	1787	Risk Ratio (IV, Random, 95% CI)	2.57 [1.00, 6.64]
1.6 Additional surgical procedures	2	1787	Risk Ratio (IV, Random, 95% CI)	1.10 [0.45, 2.67]
1.7 Blood transfusion or other blood products	2	1787	Risk Ratio (IV, Random, 95% CI)	1.47 [1.02, 2.14]
1.8 Mean additional blood loss	2	1787	Mean Difference (IV, Random, 95% CI)	42.85 [16.79, 68.90]
1.9 Fever	2	1787	Risk Ratio (IV, Random, 95% CI)	3.43 [0.65, 18.18]
1.10 Nausea	2	1787	Risk Ratio (IV, Random, 95% CI)	0.99 [0.70, 1.39]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.11 Vomiting	2	1787	Risk Ratio (IV, Random, 95% CI)	2.47 [1.37, 4.47]
1.12 Headache	2	1787	Risk Ratio (IV, Random, 95% CI)	1.05 [0.22, 4.99]
1.13 Shivering	2	1787	Risk Ratio (IV, Random, 95% CI)	2.70 [2.28, 3.19]
1.14 Diarrhoea	2	1787	Risk Ratio (IV, Random, 95% CI)	1.39 [0.44, 4.39]

Analysis 1.1. Comparison 1: Misoprostol versus oxytocin, Outcome 1: Additional blood loss of 500 mL or more

Study or Subgroup	Misoprostol Events	Misoprostol Total	Oxytocin Events	Oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Blum 2010	58	407	53	402	52.1%	1.08 [0.76 , 1.53]
Winikoff 2010	53	488	20	490	47.9%	2.66 [1.62 , 4.38]
Total (95% CI)		**895**		**892**	**100.0%**	**1.66 [0.69 , 4.02]**
Total events:	111		73			

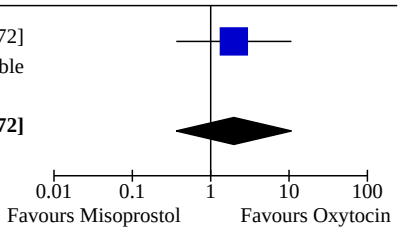
Heterogeneity: Tau² = 0.36; Chi² = 8.46, df = 1 (P = 0.004); I² = 88%
Test for overall effect: Z = 1.13 (P = 0.26)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Misoprostol versus oxytocin, Outcome 2: Composite of maternal death or severe morbidity

Study or Subgroup	Misoprostol Events	Misoprostol Total	Oxytocin Events	Oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Blum 2010	4	407	2	402	100.0%	1.98 [0.36 , 10.72]
Winikoff 2010	0	488	0	490		Not estimable
Total (95% CI)		**895**		**892**	**100.0%**	**1.98 [0.36 , 10.72]**
Total events:	4		2			

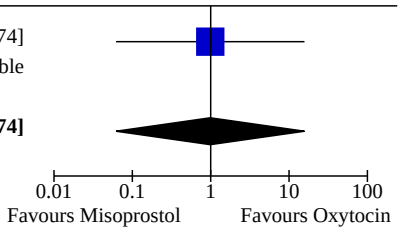
Heterogeneity: Not applicable
Test for overall effect: Z = 0.79 (P = 0.43)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Misoprostol versus oxytocin, Outcome 3: Death

Study or Subgroup	Misoprostol Events	Misoprostol Total	Oxytocin Events	Oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Blum 2010	1	407	1	402	100.0%	0.99 [0.06 , 15.74]
Winikoff 2010	0	488	0	490		Not estimable
Total (95% CI)		**895**		**892**	**100.0%**	**0.99 [0.06 , 15.74]**
Total events:	1		1			

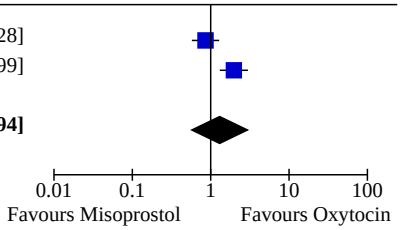
Heterogeneity: Not applicable
Test for overall effect: Z = 0.01 (P = 0.99)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Misoprostol versus oxytocin, Outcome 4: Additional uterotonics

Study or Subgroup	Misoprostol Events	Misoprostol Total	Oxytocin Events	Oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Blum 2010	40	407	46	402	50.2%	0.86 [0.58 , 1.28]
Winikoff 2010	61	488	31	490	49.8%	1.98 [1.31 , 2.99]
Total (95% CI)		**895**		**892**	**100.0%**	**1.30 [0.57 , 2.94]**
Total events:	101		77			

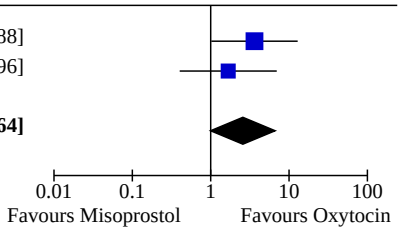
Heterogeneity: Tau² = 0.30; Chi² = 8.04, df = 1 (P = 0.005); I² = 88%
Test for overall effect: Z = 0.63 (P = 0.53)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Misoprostol versus oxytocin, Outcome 5: Additional blood loss of 1000 mL or more

Study or Subgroup	Misoprostol Events	Misoprostol Total	Oxytocin Events	Oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Blum 2010	11	407	3	402	55.8%	3.62 [1.02 , 12.88]
Winikoff 2010	5	488	3	490	44.2%	1.67 [0.40 , 6.96]
Total (95% CI)		**895**		**892**	**100.0%**	**2.57 [1.00 , 6.64]**
Total events:	16		6			

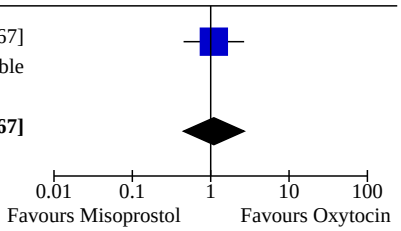
Heterogeneity: Tau² = 0.00; Chi² = 0.63, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 1.96 (P = 0.05)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Misoprostol versus oxytocin, Outcome 6: Additional surgical procedures

Study or Subgroup	Misoprostol Events	Misoprostol Total	Oxytocin Events	Oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Blum 2010	10	407	9	402	100.0%	1.10 [0.45 , 2.67]
Winikoff 2010	0	488	0	490		Not estimable
Total (95% CI)		**895**		**892**	**100.0%**	**1.10 [0.45 , 2.67]**
Total events:	10		9			

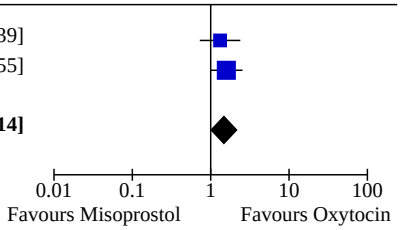
Heterogeneity: Not applicable
Test for overall effect: Z = 0.20 (P = 0.84)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Misoprostol versus oxytocin, Outcome 7: Blood transfusion or other blood products

Study or Subgroup	Misoprostol Events	Misoprostol Total	Oxytocin Events	Oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Blum 2010	24	407	18	402	38.9%	1.32 [0.73 , 2.39]
Winikoff 2010	41	488	26	490	61.1%	1.58 [0.98 , 2.55]
Total (95% CI)		**895**		**892**	**100.0%**	**1.47 [1.02 , 2.14]**
Total events:	65		44			

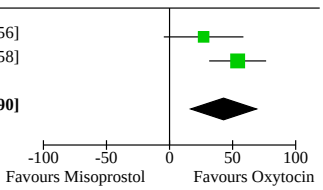
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 2.05 (P = 0.04)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: Misoprostol versus oxytocin, Outcome 8: Mean additional blood loss

Study or Subgroup	Misoprostol Mean [mL]	Misoprostol SD [mL]	Misoprostol Total	Oxytocin Mean [mL]	Oxytocin SD [mL]	Oxytocin Total	Weight	Mean Difference IV, Random, 95% CI [mL]
Blum 2010	279	251	407	252	205	402	41.3%	27.00 [-4.56 , 58.56]
Winikoff 2010	244	186	488	190	174	490	58.7%	54.00 [31.42 , 76.58]
Total (95% CI)			**895**			**892**	**100.0%**	**42.85 [16.79 , 68.90]**

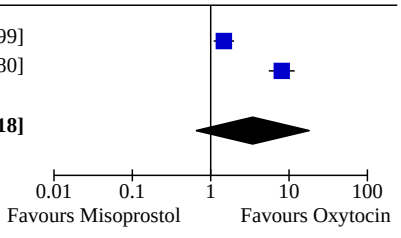
Heterogeneity: Tau² = 168.49; Chi² = 1.86, df = 1 (P = 0.17); I² = 46%
Test for overall effect: Z = 3.22 (P = 0.001)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: Misoprostol versus oxytocin, Outcome 9: Fever

Study or Subgroup	Misoprostol Events	Misoprostol Total	Oxytocin Events	Oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Blum 2010	88	407	59	402	50.2%	1.47 [1.09 , 1.99]
Winikoff 2010	217	488	27	490	49.8%	8.07 [5.52 , 11.80]
Total (95% CI)		**895**		**892**	**100.0%**	**3.43 [0.65 , 18.18]**
Total events:	305		86			

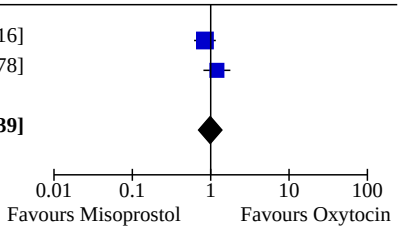
Heterogeneity: Tau² = 1.42; Chi² = 47.48, df = 1 (P < 0.00001); I² = 98%
Test for overall effect: Z = 1.45 (P = 0.15)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: Misoprostol versus oxytocin, Outcome 10: Nausea

Study or Subgroup	Misoprostol Events	Misoprostol Total	Oxytocin Events	Oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Blum 2010	59	407	69	402	55.8%	0.84 [0.61 , 1.16]
Winikoff 2010	49	488	41	490	44.2%	1.20 [0.81 , 1.78]
Total (95% CI)		**895**		**892**	**100.0%**	**0.99 [0.70 , 1.39]**
Total events:	108		110			

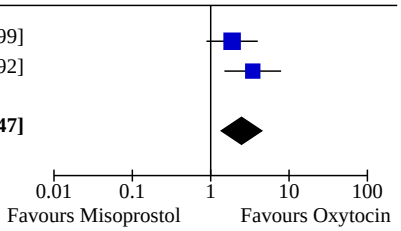
Heterogeneity: Tau² = 0.03; Chi² = 1.84, df = 1 (P = 0.18); I² = 46%
Test for overall effect: Z = 0.08 (P = 0.94)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: Misoprostol versus oxytocin, Outcome 11: Vomiting

Study or Subgroup	Misoprostol Events	Misoprostol Total	Oxytocin Events	Oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Blum 2010	19	407	10	402	54.4%	1.88 [0.88 , 3.99]
Winikoff 2010	24	488	7	490	45.6%	3.44 [1.50 , 7.92]
Total (95% CI)		**895**		**892**	**100.0%**	**2.47 [1.37 , 4.47]**
Total events:	43		17			

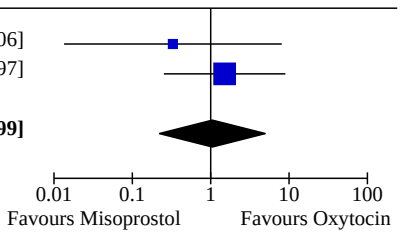
Heterogeneity: Tau² = 0.02; Chi² = 1.12, df = 1 (P = 0.29); I² = 11%
Test for overall effect: Z = 3.00 (P = 0.003)
Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1: Misoprostol versus oxytocin, Outcome 12: Headache

Study or Subgroup	Misoprostol Events	Misoprostol Total	Oxytocin Events	Oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Blum 2010 (1)	0	407	1	402	23.8%	0.33 [0.01 , 8.06]
Winikoff 2010 (1)	3	488	2	490	76.2%	1.51 [0.25 , 8.97]
Total (95% CI)		**895**		**892**	**100.0%**	**1.05 [0.22 , 4.99]**
Total events:	3		3			

Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.06 (P = 0.95)
Test for subgroup differences: Not applicable



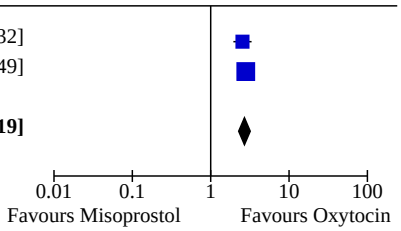
Footnotes

(1) Retrieved data from Mousa HA et al. 2014.

Analysis 1.13. Comparison 1: Misoprostol versus oxytocin, Outcome 13: Shivering

Study or Subgroup	Misoprostol Events	Misoprostol Total	Oxytocin Events	Oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Blum 2010	152	407	59	402	40.2%	2.54 [1.95 , 3.32]
Winikoff 2010	229	488	82	490	59.8%	2.80 [2.25 , 3.49]
Total (95% CI)		**895**		**892**	**100.0%**	**2.70 [2.28 , 3.19]**
Total events:	381		141			

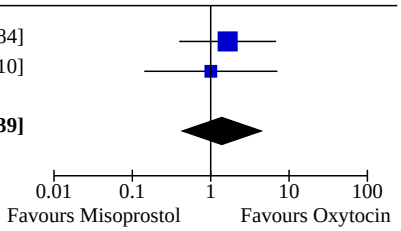
Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 11.48 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.14. Comparison 1: Misoprostol versus oxytocin, Outcome 14: Diarrhoea

Study or Subgroup	Misoprostol Events	Misoprostol Total	Oxytocin Events	Oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Blum 2010	5	407	3	402	65.3%	1.65 [0.40 , 6.84]
Winikoff 2010	2	488	2	490	34.7%	1.00 [0.14 , 7.10]
Total (95% CI)		**895**		**892**	**100.0%**	**1.39 [0.44 , 4.39]**
Total events:	7		5			

Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 1 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.56 (P = 0.58)
Test for subgroup differences: Not applicable



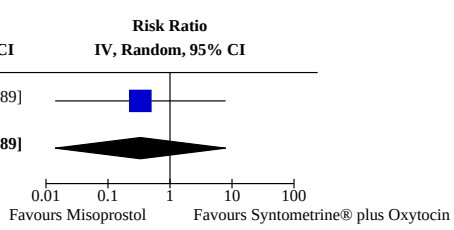
Comparison 2. Misoprostol versus Syntometrine® plus oxytocin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Composite of maternal death or severe morbidity	1	64	Risk Ratio (IV, Random, 95% CI)	0.33 [0.01, 7.89]
2.2 Additional uterotonics	1	64	Risk Ratio (IV, Random, 95% CI)	0.18 [0.04, 0.76]
2.3 Additional surgical procedures	1	64	Risk Ratio (IV, Random, 95% CI)	0.67 [0.12, 3.73]

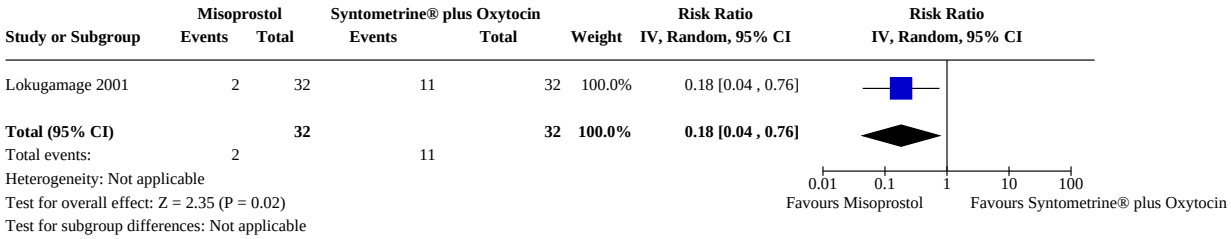
Analysis 2.1. Comparison 2: Misoprostol versus Syntometrine® plus oxytocin, Outcome 1: Composite of maternal death or severe morbidity

Study or Subgroup	Misoprostol Events	Misoprostol Total	Syntometrine® plus Oxytocin Events	Syntometrine® plus Oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Lokugamage 2001	0	32	1	32	100.0%	0.33 [0.01 , 7.89]
Total (95% CI)		**32**		**32**	**100.0%**	**0.33 [0.01 , 7.89]**
Total events:	0		1			

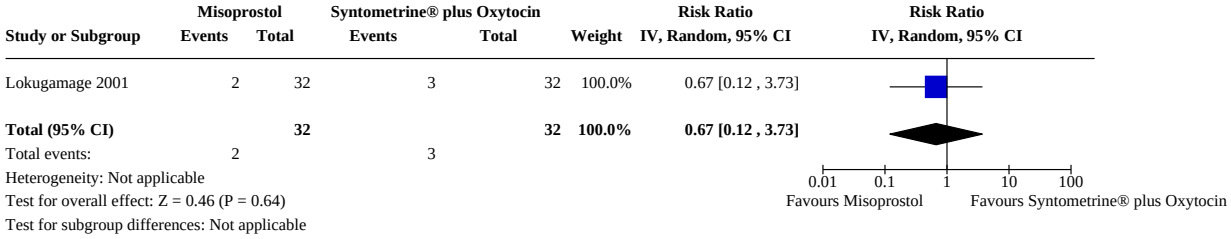
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Misoprostol versus Syntometrine® plus oxytocin, Outcome 2: Additional uterotonics



Analysis 2.3. Comparison 2: Misoprostol versus Syntometrine® plus oxytocin, Outcome 3: Additional surgical procedures



Comparison 3. Misoprostol plus oxytocin versus oxytocin

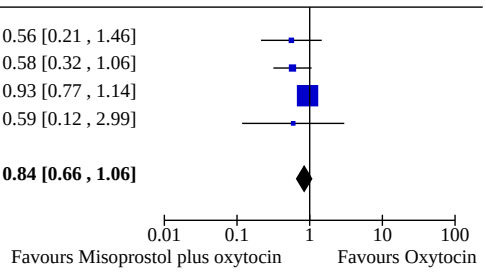
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Additional blood loss of 500 mL or more	4	1873	Risk Ratio (IV, Random, 95% CI)	0.84 [0.66, 1.06]
3.2 Composite of maternal death or severe morbidity	4	1881	Risk Ratio (IV, Random, 95% CI)	1.09 [0.35, 3.39]
3.3 Death	4	1881	Risk Ratio (IV, Random, 95% CI)	6.10 [0.73, 50.59]
3.4 Additional uterotonics	4	1866	Risk Ratio (IV, Random, 95% CI)	0.99 [0.94, 1.05]
3.5 Additional blood loss of 1000 mL or more	4	1873	Risk Ratio (IV, Random, 95% CI)	0.76 [0.43, 1.34]
3.6 Additional surgical procedures	4	1881	Risk Ratio (IV, Random, 95% CI)	0.65 [0.21, 2.00]
3.7 Blood transfusion or other blood products	4	1877	Risk Ratio (IV, Random, 95% CI)	0.95 [0.77, 1.17]
3.8 Mean additional blood loss	4	1873	Mean Difference (IV, Random, 95% CI)	-14.59 [-38.47, 9.30]
3.9 Change in haemoglobin	1	61	Mean Difference (IV, Random, 95% CI)	-2.00 [-8.29, 4.29]
3.10 Fever	4	1866	Risk Ratio (IV, Random, 95% CI)	3.07 [2.62, 3.61]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.11 Nausea	3	1642	Risk Ratio (IV, Random, 95% CI)	1.19 [0.84, 1.68]
3.12 Vomiting	2	1482	Risk Ratio (IV, Random, 95% CI)	1.85 [1.16, 2.95]
3.13 Headache	3	1642	Risk Ratio (IV, Random, 95% CI)	1.12 [0.65, 1.93]
3.14 Shivering	4	1876	Risk Ratio (IV, Random, 95% CI)	2.25 [1.77, 2.86]
3.15 Diarrhoea	2	1482	Risk Ratio (IV, Random, 95% CI)	1.22 [0.37, 3.99]

Analysis 3.1. Comparison 3: Misoprostol plus oxytocin versus oxytocin, Outcome 1: Additional blood loss of 500 mL or more

Study or Subgroup	Misoprostol plus oxytocin Events	Total	Oxytocin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Hofmeyr 2004	6	117	11	120	5.9%	0.56 [0.21 , 1.46]
Walraven 2004	13	79	23	81	14.2%	0.58 [0.32 , 1.06]
Widmer 2010	149	703	162	714	77.8%	0.93 [0.77 , 1.14]
Zuberi 2008	2	27	4	32	2.1%	0.59 [0.12 , 2.99]
Total (95% CI)		**926**		**947**	**100.0%**	**0.84 [0.66 , 1.06]**
Total events:	170		200			

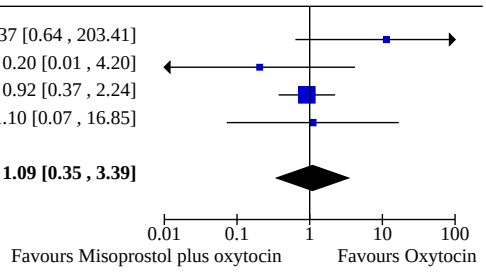
Heterogeneity: Tau² = 0.01; Chi² = 3.26, df = 3 (P = 0.35); I² = 8%
Test for overall effect: Z = 1.45 (P = 0.15)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Misoprostol plus oxytocin versus oxytocin, Outcome 2: Composite of maternal death or severe morbidity

Study or Subgroup	Misoprostol plus oxytocin Events	Total	Oxytocin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Hofmeyr 2004	5	117	0	121	13.3%	11.37 [0.64 , 203.41]
Walraven 2004	0	79	2	81	12.2%	0.20 [0.01 , 4.20]
Widmer 2010	9	705	10	717	59.9%	0.92 [0.37 , 2.24]
Zuberi 2008	1	29	1	32	14.6%	1.10 [0.07 , 16.85]
Total (95% CI)		**930**		**951**	**100.0%**	**1.09 [0.35 , 3.39]**
Total events:	15		13			

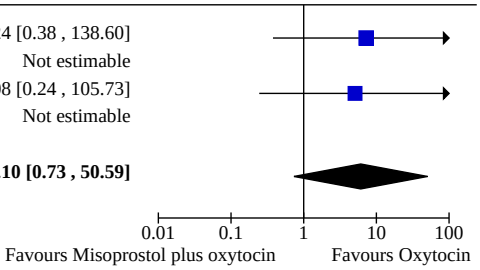
Heterogeneity: Tau² = 0.35; Chi² = 3.83, df = 3 (P = 0.28); I² = 22%
Test for overall effect: Z = 0.16 (P = 0.88)
Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3: Misoprostol plus oxytocin versus oxytocin, Outcome 3: Death

Study or Subgroup	Misoprostol plus oxytocin Events	Total	Oxytocin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Hofmeyr 2004	3	117	0	121	51.4%	7.24 [0.38 , 138.60]
Walraven 2004 (1)	0	79	0	81		Not estimable
Widmer 2010	2	705	0	717	48.6%	5.08 [0.24 , 105.73]
Zuberi 2008	0	29	0	32		Not estimable
Total (95% CI)		**930**		**951**	**100.0%**	**6.10 [0.73 , 50.59]**
Total events:	5		0			

Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%
Test for overall effect: Z = 1.67 (P = 0.09)
Test for subgroup differences: Not applicable

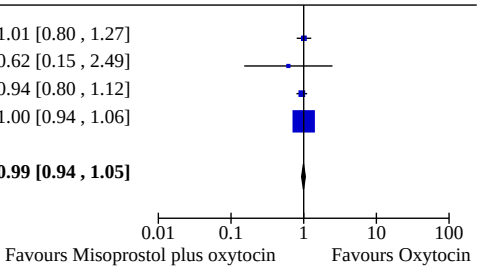


Footnotes
(1) Retrieved data from Mousa HA et al. 2014.

Analysis 3.4. Comparison 3: Misoprostol plus oxytocin versus oxytocin, Outcome 4: Additional uterotonics

Study or Subgroup	Misoprostol plus oxytocin Events	Total	Oxytocin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Hofmeyr 2004	63	111	63	112	6.1%	1.01 [0.80 , 1.27]
Walraven 2004	3	79	5	81	0.2%	0.62 [0.15 , 2.49]
Widmer 2010	188	705	203	717	11.4%	0.94 [0.80 , 1.12]
Zuberi 2008	29	29	32	32	82.3%	1.00 [0.94 , 1.06]
Total (95% CI)		**924**		**942**	**100.0%**	**0.99 [0.94 , 1.05]**
Total events:	283		303			

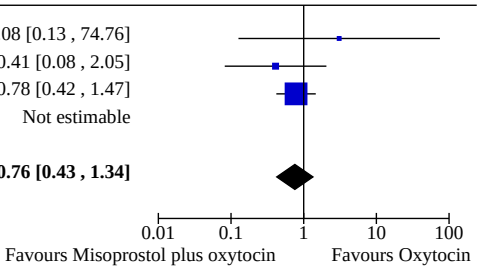
Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 3 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)
Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3: Misoprostol plus oxytocin versus oxytocin, Outcome 5: Additional blood loss of 1000 mL or more

Study or Subgroup	Misoprostol plus oxytocin Events	Total	Oxytocin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Hofmeyr 2004	1	117	0	120	3.2%	3.08 [0.13 , 74.76]
Walraven 2004	2	79	5	81	12.6%	0.41 [0.08 , 2.05]
Widmer 2010	17	703	22	714	84.1%	0.78 [0.42 , 1.47]
Zuberi 2008 (1)	0	27	0	32		Not estimable
Total (95% CI)		**926**		**947**	**100.0%**	**0.76 [0.43 , 1.34]**
Total events:	20		27			

Heterogeneity: Tau² = 0.00; Chi² = 1.31, df = 2 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.96 (P = 0.34)
Test for subgroup differences: Not applicable

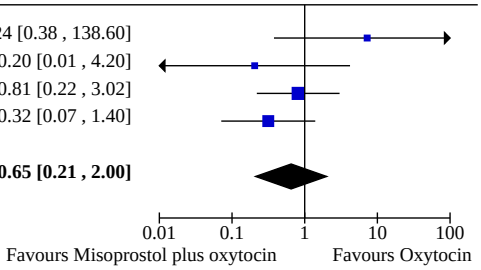


Footnotes
(1) Retrieved data from Mousa HA et al. 2014.

Analysis 3.6. Comparison 3: Misoprostol plus oxytocin versus oxytocin, Outcome 6: Additional surgical procedures

Study or Subgroup	Misoprostol plus oxytocin Events	Total	Oxytocin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Hofmeyr 2004	3	117	0	121	12.5%	7.24 [0.38 , 138.60]
Walraven 2004	0	79	2	81	12.0%	0.20 [0.01 , 4.20]
Widmer 2010 (1)	4	705	5	717	40.5%	0.81 [0.22 , 3.02]
Zuberi 2008	2	29	7	32	34.9%	0.32 [0.07 , 1.40]
Total (95% CI)		**930**		**951**	**100.0%**	**0.65 [0.21 , 2.00]**
Total events:	9		14			

Heterogeneity: Tau² = 0.37; Chi² = 4.13, df = 3 (P = 0.25); I² = 27%
Test for overall effect: Z = 0.75 (P = 0.45)
Test for subgroup differences: Not applicable

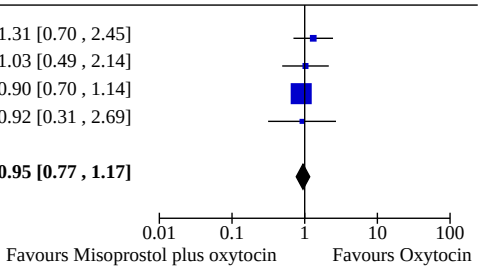


Footnotes
(1) Retrived data from Mousa HA et al. 2014.

Analysis 3.7. Comparison 3: Misoprostol plus oxytocin versus oxytocin, Outcome 7: Blood transfusion or other blood products

Study or Subgroup	Misoprostol plus oxytocin Events	Total	Oxytocin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Hofmeyr 2004	19	115	15	119	11.5%	1.31 [0.70 , 2.45]
Walraven 2004	12	79	12	81	8.3%	1.03 [0.49 , 2.14]
Widmer 2010	103	705	117	717	76.3%	0.90 [0.70 , 1.14]
Zuberi 2008	5	29	6	32	3.9%	0.92 [0.31 , 2.69]
Total (95% CI)		**928**		**949**	**100.0%**	**0.95 [0.77 , 1.17]**
Total events:	139		150			

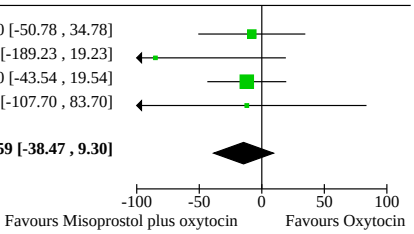
Heterogeneity: Tau² = 0.00; Chi² = 1.29, df = 3 (P = 0.73); I² = 0%
Test for overall effect: Z = 0.50 (P = 0.62)
Test for subgroup differences: Not applicable



Analysis 3.8. Comparison 3: Misoprostol plus oxytocin versus oxytocin, Outcome 8: Mean additional blood loss

Study or Subgroup	Misoprostol plus oxytocin Mean [mL]	SD [mL]	Total	Oxytocin Mean [mL]	SD [mL]	Total	Weight	Mean Difference IV, Random, 95% CI [mL]
Hofmeyr 2004	168	163	117	176	173	120	31.2%	-8.00 [-50.78 , 34.78]
Walraven 2004	325	264	79	410	397	81	5.3%	-85.00 [-189.23 , 19.23]
Widmer 2010	320	270	703	332	333	714	57.3%	-12.00 [-43.54 , 19.54]
Zuberi 2008	175	168	27	187	207	32	6.2%	-12.00 [-107.70 , 83.70]
Total (95% CI)			**926**			**947**	**100.0%**	**-14.59 [-38.47 , 9.30]**

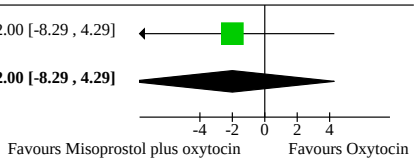
Heterogeneity: Tau² = 0.00; Chi² = 1.87, df = 3 (P = 0.60); I² = 0%
Test for overall effect: Z = 1.20 (P = 0.23)
Test for subgroup differences: Not applicable



Analysis 3.9. Comparison 3: Misoprostol plus oxytocin versus oxytocin, Outcome 9: Change in haemoglobin

Study or Subgroup	Misoprostol plus oxytocin Mean [g/L]	SD [g/L]	Total	Oxytocin Mean [g/L]	SD [g/L]	Total	Weight	Mean Difference IV, Random, 95% CI [g/L]
Zuberi 2008	20	11	29	22	14	32	100.0%	-2.00 [-8.29 , 4.29]
Total (95% CI)			**29**			**32**	**100.0%**	**-2.00 [-8.29 , 4.29]**

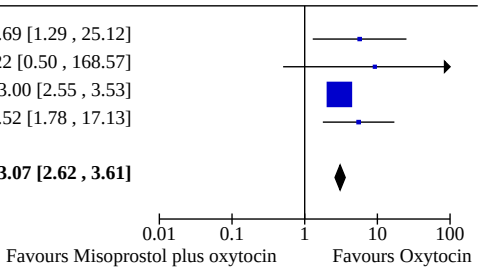
Heterogeneity: Not applicable
Test for overall effect: Z = 0.62 (P = 0.53)
Test for subgroup differences: Not applicable



Analysis 3.10. Comparison 3: Misoprostol plus oxytocin versus oxytocin, Outcome 10: Fever

Study or Subgroup	Misoprostol plus oxytocin Events	Total	Oxytocin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Hofmeyr 2004 (1)	11	114	2	118	1.2%	5.69 [1.29 , 25.12]
Walraven 2004 (2)	4	79	0	81	0.3%	9.22 [0.50 , 168.57]
Widmer 2010	406	702	137	711	96.5%	3.00 [2.55 , 3.53]
Zuberi 2008 (3)	15	29	3	32	2.0%	5.52 [1.78 , 17.13]
Total (95% CI)		**924**		**942**	**100.0%**	**3.07 [2.62 , 3.61]**
Total events:	436		142			

Heterogeneity: Tau² = 0.00; Chi² = 2.32, df = 3 (P = 0.51); I² = 0%
Test for overall effect: Z = 13.72 (P < 0.00001)
Test for subgroup differences: Not applicable

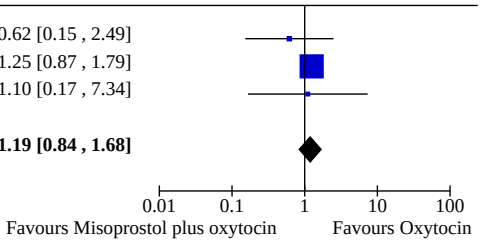


Footnotes
(1) The threshold here was 38.5
(2) Retrieved data from Mousa HA et al. 2014.
(3) The threshold here was 37.5

Analysis 3.11. Comparison 3: Misoprostol plus oxytocin versus oxytocin, Outcome 11: Nausea

Study or Subgroup	Misoprostol plus oxytocin Events	Total	Oxytocin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Walraven 2004	3	79	5	81	6.1%	0.62 [0.15 , 2.49]
Widmer 2010	60	704	49	717	90.6%	1.25 [0.87 , 1.79]
Zuberi 2008	2	29	2	32	3.3%	1.10 [0.17 , 7.34]
Total (95% CI)		**812**		**830**	**100.0%**	**1.19 [0.84 , 1.68]**
Total events:	65		56			

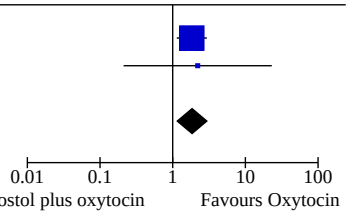
Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.99 (P = 0.32)
Test for subgroup differences: Not applicable



Analysis 3.12. Comparison 3: Misoprostol plus oxytocin versus oxytocin, Outcome 12: Vomiting

Study or Subgroup	Misoprostol plus oxytocin Events	Total	Oxytocin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Widmer 2010	45	704	25	717	96.0%	1.83 [1.14 , 2.96]
Zuberi 2008	2	29	1	32	4.0%	2.21 [0.21 , 23.08]
Total (95% CI)		**733**		**749**	**100.0%**	**1.85 [1.16 , 2.95]**
Total events:	47		26			

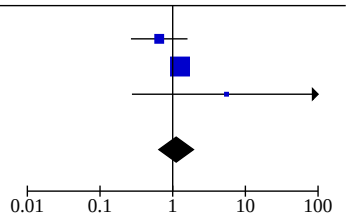
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 2.57 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 3.13. Comparison 3: Misoprostol plus oxytocin versus oxytocin, Outcome 13: Headache

Study or Subgroup	Misoprostol plus oxytocin Events	Total	Oxytocin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Walraven 2004	7	79	11	81	25.7%	0.65 [0.27 , 1.60]
Widmer 2010 (1)	125	704	101	717	71.1%	1.26 [0.99 , 1.60]
Zuberi 2008	2	29	0	32	3.2%	5.50 [0.27 , 110.01]
Total (95% CI)		**812**		**830**	**100.0%**	**1.12 [0.65 , 1.93]**
Total events:	134		112			

Heterogeneity: Tau² = 0.09; Chi² = 2.92, df = 2 (P = 0.23); I² = 31%
Test for overall effect: Z = 0.39 (P = 0.69)
Test for subgroup differences: Not applicable

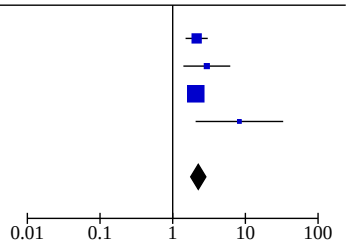


Footnotes
(1) Retrieved data from Mousa HA et al. 2014.

Analysis 3.14. Comparison 3: Misoprostol plus oxytocin versus oxytocin, Outcome 14: Shivering

Study or Subgroup	Misoprostol plus oxytocin Events	Total	Oxytocin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Hofmeyr 2004	63	116	30	118	27.8%	2.14 [1.50 , 3.04]
Walraven 2004	23	79	8	81	9.1%	2.95 [1.40 , 6.19]
Widmer 2010	514	704	252	717	60.2%	2.08 [1.86 , 2.32]
Zuberi 2008	15	29	2	32	2.9%	8.28 [2.07 , 33.13]
Total (95% CI)		**928**		**948**	**100.0%**	**2.25 [1.77 , 2.86]**
Total events:	615		292			

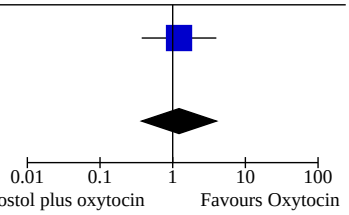
Heterogeneity: Tau² = 0.02; Chi² = 4.59, df = 3 (P = 0.20); I² = 35%
Test for overall effect: Z = 6.62 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.15. Comparison 3: Misoprostol plus oxytocin versus oxytocin, Outcome 15: Diarrhoea

Study or Subgroup	Misoprostol plus oxytocin Events	Total	Oxytocin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Widmer 2010	6	704	5	717	100.0%	1.22 [0.37 , 3.99]
Zuberi 2008	0	29	0	32		Not estimable
Total (95% CI)		**733**		**749**	**100.0%**	**1.22 [0.37 , 3.99]**
Total events:	6		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Indirect comparison: misoprostol plus oxytocin versus misoprostol

Patient or population: women in the third stage of labour with PPH
Interventions: misoprostol plus oxytocin
Comparison/Standard care (reference): misoprostol
Outcome: multiple outcomes
Setting: hospital

Outcome	Anticipated absolute effects* (95% CI)			Indirect evidence	
	Risk with standard care	Risk with intervention	Risk difference with intervention	RR (95% CI)	Certainty
Additional blood loss of 500 mL or more	136 per 1000 (misoprostol)	69 per 1000 (misoprostol plus oxytocin)	67 fewer per 1000 (from 109 fewer to 35 more) with misoprostol plus oxytocin compared with misoprostol alone	0.51 (0.20 to 1.26)	⊕⊕⊖⊖ LOW[a]
Composite of death or severe morbidity	4 per 1000 (misoprostol)	2 per 1000 (misoprostol plus oxytocin)	2 fewer per 1000 (from 4 fewer to 13 more) with misoprostol plus oxytocin compared with misoprostol alone	0.55 (0.07 to 4.24)	⊕⊕⊖⊖ LOW[b]
Use of additional uterotonics	112 per 1000 (misoprostol)	85 per 1000 (misoprostol plus oxytocin)	27 fewer per 1000 (from 75 fewer to 82 more) with misoprostol plus oxytocin compared with misoprostol alone	0.76 (0.33 to 1.73)	⊕⊕⊖⊖ LOW[a]
Additional blood loss of 1000 mL or more	18 per 1000 (misoprostol)	5 per 1000 (misoprostol plus oxytocin)	13 fewer per 1000(from 2 fewer to 16 fewer) with misoprostol plus oxytocin compared with misoprostol alone	0.30 (0.10 to 0.89)	⊕⊕⊖⊖ LOW[b]
Blood transfusion or other blood products	72 per 1000 (misoprostol)	47 per 1000 (misoprostol plus oxytocin)	25 fewer per 1000 (from 1 fewer to 42 fewer) with misoprostol plus oxytocin compared with misoprostol alone	0.65 (0.42 to 0.99)	⊕⊕⊕⊖ MODERATE[c]

Table 1. Indirect comparison: misoprostol plus oxytocin versus misoprostol *(Continued)*

Fever	331 per 1000 (misoprostol)	298 per 1000 (misoprostol plus oxytocin)	33 fewer per 1000 (from 275 fewer to 1248 more) with misoprostol plus oxytocin compared with misoprostol alone	0.90 (0.17 to 4.77)	⊕⊕⊖⊖ LOW[a]
Vomiting	47 per 1000 (misoprostol)	35 per 1000(misoprostol plus oxytocin)	12 fewer per 1000 (from 31 fewer to 28 more) with misoprostol plus oxytocin compared with misoprostol alone	0.75 (0.35 to 1.59)	⊕⊕⊕⊕ HIGH

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] Indirect evidence downgraded -2 due to severe unexplained statistical heterogeneity and serious imprecision.
[b] Indirect evidence downgraded -2 due to very serious imprecision.
[c] Indirect evidence downgraded -1 due to indirectness.

APPENDICES

Appendix 1. Search terms for ClinicalTrials.gov and ICTRP

The WHO International Clinical Trials Registry Platform (ICTRP)

We ran each line separately
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

Third stage AND labo(u)r AND carboprost

Third stage AND labo(u)r AND syntometrine
uterotonic* AND oxytocin
uterotonic* AND misoprostol
uterotonic* AND carbetocin
uterotonic* AND ergometrine

uterotonic* AND syntometrine

uterotonic* AND carboprost
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

h(a)emorrhage AND postpartum AND syntometrine

h(a)emorrhage AND postpartum AND carboprost

ClinicalTrials.gov

Advanced search

Intervention studies

Condition = postpartum hemorrhage (taken from their index terms).

Appendix 2. Network Meta-Analysis Methods

We were able to perform standard pairwise meta-analysis where at least two trials comparing directly the same two treatment interventions reported results on a given outcome of interest. We performed indirect comparisons where two competing treatment interventions could be compared indirectly through a common comparison. All relevant methods for standard pairwise meta-analyses and indirect comparisons are thoroughly described in the main text of this review (see Methods). In this section, we present exclusively the methods that will be applied in future updates to conduct a network meta-analysis.

Unit of analysis issues

Multi-arm trials

We plan to include multi-arm trials and we will account for the correlation between the effect sizes in the network meta-analysis.

Assessment of transitivity across network treatment comparisons

In order to conduct a network meta-analysis we consider that the assumption of transitivity across treatment comparisons is likely to hold, when treatment interventions are similar in different trials (e.g. oxytocin is administered in a similar way irrespectively of the competing intervention), and pairwise comparisons do not differ in respect of effect modifier distribution (e.g. similar trial designs). Therefore, we will evaluate the presence of clinical and methodological heterogeneity within pairwise comparisons by describing and comparing the study population characteristics across all included trials.

Data synthesis

Methods for network treatment comparisons

We will first generate and assess the network diagrams to determine whether a network meta-analysis is feasible. We will then perform the network meta-analysis within a frequentist framework using multivariate meta-analysis estimated by restricted maximum likelihood. All analyses will be done using Stata statistical software and the network suite of Stata commands designed for this purpose (White 2012; White 2015).

Assessment of statistical heterogeneity across the network

Assumptions when estimating heterogeneity

For the network meta-analysis, we will assume a common estimate for heterogeneity across the different comparisons.

Measures and tests for heterogeneity

We will assess statistically the presence of heterogeneity in the entire network based on the magnitude of the heterogeneity variance parameter (T^2) estimated from the multivariate meta-analysis model. The magnitude of the heterogeneity variance will be compared to empirical distributions for dichotomous and continuous variables (Rhodes 2015; Turner 2012).

Assessment of statistical inconsistency across the network

The statistical agreement between various sources of evidence in a network of interventions should be evaluated by global and local approaches in tandem with the evaluation of clinical homogeneity.

Local approaches for evaluation inconsistency

To evaluate the presence of inconsistency locally we will use the node-splitting approach. The node-splitting technique allows two distinct components - direct evidence from direct comparisons or multi-arm trials and indirect evidence based on the remaining information (Dias 2010). The technique will be applied to all comparisons in the network and allow generation of graphics showing the difference between combined information, direct and indirect comparisons.

Global approaches for evaluation inconsistency

To evaluate consistency in the entire network simultaneously, we will use the 'design by treatment' interaction model as described by Higgins 2012, which will be implemented in STATA. This method accounts for different sources of inconsistency that can occur when studies with different designs (two-arm trials versus three-arm trials) give different results, as well as for disagreement between direct and indirect evidence. Using this approach, we will infer the presence of inconsistency from any source in the entire network based on a Chi^2 test.

Investigation of heterogeneity and inconsistency across the network

If sufficient data are available, we will perform subgroup analyses by using the following factors as possible sources of heterogeneity and/or inconsistency for both primary and secondary outcomes.

• Population: mode of delivery; prior PPH risk (high or low); setting (hospital delivery or community delivery including home birth).

• Intervention: dosage; route.

• Randomisation unit: cluster versus individual.

• Funding source: risk of bias.

• Methods of blood loss measurement: risk of bias.

• Overall risk of bias by type of outcome.

If these subgroup analyses do explain the heterogeneity/inconsistency we will note that the results should be treated with caution.

Subgroup analysis

Regardless of heterogeneity and/or inconsistency, for the primary outcomes, we will perform the following subgroup analyses by evaluating the relative effects and assessment of model fit.
• Mode of delivery (vaginal versus caesarean delivery).
• Prior PPH risk (low versus high risk).
• Setting (hospital versus community births).
• Intervention: dosage and route.
• Uterotonic administration prior to enrolment.
• Co-interventions (e.g. tranexamic acid, uterine massage).

Measures of treatment effect

Relative treatment ranking

We intend to estimate the cumulative probabilities for each uterotonic agent being at each possible rank and obtain a treatment hierarchy using the surface under the cumulative ranking curve (SUCRA); the larger the SUCRA the higher its rank among all available agents (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. Rankings are constructed drawing 1000 samples from their approximate posterior density. For each draw, the linear predictor is evaluated for each study, and the largest linear predictor would have been noted (White 2011).

Summary of findings

We will assess the certainty of the network evidence based on the certainty ratings of the corresponding direct and indirect comparisons.

- When results from direct and indirect comparisons are coherent, the higher certainty rating of the two will be chosen.
- When results from direct and indirect comparisons are incoherent the certainty rating of the dominant comparison (i.e. the most precise estimate) will be chosen and further downgraded once.

When the network estimate is precise, the certainty rating will be upgraded once if it was previously rated down for imprecision due to wide confidence intervals. When the network estimate is imprecise, the certainty rating will be downgraded once only if it was not previously rated down for the same reason (Brignardello-Petersen 2018; Puhan 2014).

HISTORY

Protocol first published: Issue 8, 2017
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CONTRIBUTIONS OF AUTHORS

Ioannis D Gallos (IDG) and Arri Commarasamy (AC) conceived the idea for this study. William R Parry-Smith (WRPS) drafted the protocol. WRPS, Argyro Papadopoulou (AP) screened trials, extracted data and performed pairwise statistical analyses. IDG and AP graded the evidence. Shireen Meher (SM) screened trials and extracted data. Malcolm J Price (MJP), Mariana Widmer (MW), Aurelio Tobias (AT), Zarko Alfirevic (ZA), Andrew Weeks (AW), G Justus Hofmeyr (GJH), A Metin Gülmezoglu (AMG), IDG and AC designed the analysis. AT and MJP provided statistical advice and input. IDG, AP, WRPS, ET, MW, MJP, AT, SM, AW, GJH, Olufemi T Oladapo (OTO), Joshua Vogel (JV), Fernando Althabe (FA) AC edited and revised the review.

DECLARATIONS OF INTEREST

William R Parry-Smith (WRPS) is an Executive Board member of AmmaLife (UK registered charity 1120236), and a member of The UK Membership Board of The Royal College of Obstetricians and Gynaecologists (UK registered charity 213280). He was also a Trustee of Baby Lifeline (UK registered charity 1006457) until April 2019. He does not receive payment for these roles but has received payment from these organisations for travel for activities not related to this review. He has also received payment from the Liverpool School of Tropical Medicine for an invited lecture on cervical cancer and women's health. AmmaLife contributed to this review by funding literature/library costs.

Argyro Papadopoulou (AP): none known.

Eleanor Thomas (ET): none known.

Aurelio Tobias (AT): none known.

Malcolm J Price (MJP): none known.

Shireen Meher (SM): none known.

Zarko Alfirevic (ZA): none known.

Andrew Weeks (AW): voluntarily runs the not-for-profit misoprostol.org website that provides information about the optimal doses of misoprostol, including for the treatment of PPH. He also has two large clinical trial grants (from NIHR) on PPH treatment. These studies could potentially be eligible for inclusion in subsequent updates of this review, but he will not participate in decisions regarding these trials. He is also a consultant to Gynuity Health projects (unpaid) and to Azanta A/S and Monash University (both pay consultancy fees to his institution (University of Liverpool). He is also the inventor of the PPH Butterfly device and one of the inventors of the LifeStart neonatal resuscitation trolley. He may in future receive personal payments in connection to the PPH Butterfly for which the University of Liverpool holds the patent.

G Justus Hofmeyr (GJH): is an author of trials included in the review. GJH did not participate in decisions regarding these trials.

A Metin Gülmezoglu (AMG): none known.

Mariana Widmer (MW): is an author of trials included in the review. MW did not participate in decisions regarding these trials.

Olufemi T Oladapo (OTO): none known.

Joshua Vogel (JV): none known.

Fernando Althabe (FA): none known.

Arri Coomarasamy (AC): is the founder of Ammalife (UK registered charity 1120236), and remains an active member of the Executive Board of this organisation. He does not receive any payment for this relationship.

Ioannis D Gallos (IDG): none known.

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Internal sources

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- JN Medical College Belgaum, India

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- University of Liverpool, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We were not able to produce a network meta-analysis as there were too few trials comparing the available uterotonic agents to produce a connected network. We were not able to proceed with the network methods outlined in the protocol, specifically it was impossible to produce a meaningful hierarchy of first-line uterotonic agents for the treatment of PPH. We were also unable to perform the prespecified subgroup and sensitivity analyses.

Methods for direct treatment comparison

We used RevMan 5.3 to estimate all direct treatment comparisons rather than in STATA as suggested in the protocol.

Methods for indirect treatment comparison

We used the method described by Bucher to produce indirect comparisons for the most relevant agents and outcomes-misoprostol plus oxytocin versus misoprostol alone via oxytocin (Bucher 1997). The indirect comparisons were estimated using Excel as described by our co-author Aurelio Tobias (Tobias 2014).

INDEX TERMS

Medical Subject Headings (MeSH)

Bias; Blood Transfusion [statistics & numerical data]; Confidence Intervals; Drug Therapy, Combination [methods]; Ergonovine [*therapeutic use]; Misoprostol [adverse effects] [*therapeutic use]; *Network Meta-Analysis; Oxytocics [adverse effects] [*therapeutic use]; Oxytocin [adverse effects] [*therapeutic use]; Postpartum Hemorrhage [chemically induced] [*drug therapy] [mortality]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy