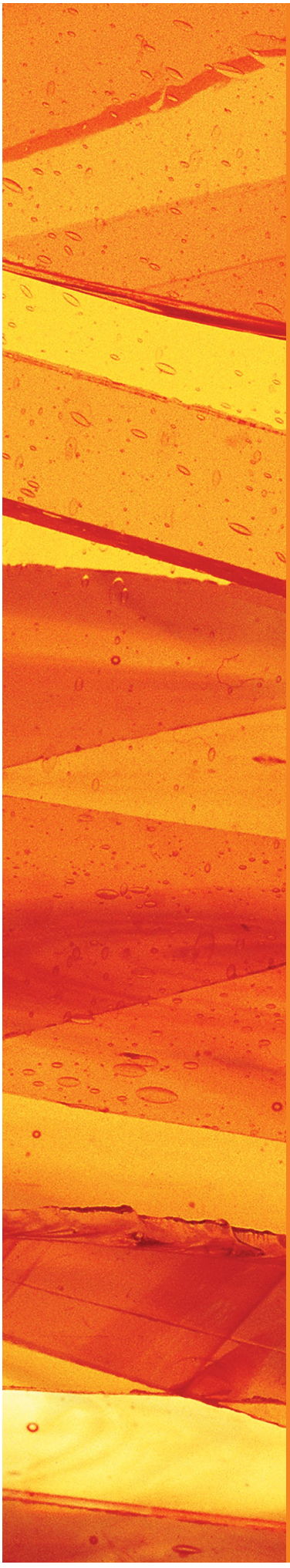

WHO recommendations

Uterotonics for the prevention of postpartum haemorrhage

Web annex 7: Choice of uterotonic agents

EVIDENCE TO DECISION FRAMEWORK

World Health Organization

WHO recommendations

Uterotonics for the prevention of postpartum haemorrhage

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Evidence to Decision framework

World Health Organization

WHO/RHR/18.34

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This publication forms part of the WHO guideline entitled WHO recommendations: Uterotonics for the prevention of postpartum haemorrhage. It is being made publicly available as supplied by those responsible for its development for transparency purposes and information, as required by WHO (see the WHO handbook for guideline development, 2nd edition (2014)).

Contents

1. Background

Characteristics	Oxytocin	Carbetocin	Misoprostol	Injectable prostaglandins	Ergometrine	Oxytocin plus ergometrine	Misoprostol plus oxytocin
Brief description *(1,2)*	Synthetic cyclic peptide form of the naturally occurring posterior pituitary hormone Binds to oxytocin receptors in the myometrium, stimulating contraction of this uterine smooth muscle by increasing the sodium permeability of its myofibrils	Long-acting synthetic analogue of oxytocin with agonist properties Binds to oxytocin receptors in the uterine smooth muscle, resulting in rhythmic contractions, increased frequency of existing contractions, and increased uterine tone	Synthetic analogue of natural prostaglandin E1 Has oxytocic properties, inhibits gastric acid and pepsin secretion, and enhances gastric mucosal resistance to injury	Injectable prostaglandins (systemic) trialled for PPH prevention include prostaglandin F2α analogues (carboprost), prostaglandin E2 (dinoprostone) and prostaglandin E2 analogues (sulprostone)	Ergometrine and methylergometrine are ergot alkaloids that increase uterine muscle tone by causing sustained uterine contractions	Fixed drug combination – oxytocin (5 IU) plus ergometrine (500 μg)	See misoprostol and oxytocin. Combination agents not in synthetic (fixed-dose) or naturally occurring forms
Pharmacokinetics *(1,2)*	IV: almost immediate action with peak concentration after 30 minutes IM: slower onset of action, taking 3–7 minutes, but produces a longer-lasting clinical effect of up to 1 hour Half-life: 1–6 minutes.	IV: sustained uterine contractions within 2 minutes, lasting for about 6 minutes and followed by rhythmic contractions for 60 minutes IM: sustained uterine contractions last for about 11 minutes and rhythmic contractions for 120 minutes Half-life: 40 minutes.	Absorbed 9–15 minutes after sublingual, oral, vaginal or rectal use Oral and sublingual routes have the advantage of rapid onset of action, while the vaginal and rectal routes result in prolonged activity and greater bioavailability Half-life: 20–40 minutes	IM: 15–60 minutes to peak plasma concentration Half-life: 8 minutes	IM: onset of action within 2–3 minutes, lasting for about 3 hours IV: onset of action within 1 minute, lasting 45 minutes (although rhythmic contractions may persist for up to 3 hours) Half-life: 30–120 minutes	See oxytocin and ergometrine IM: latent period for uterine response is about 2.5 minutes; uterotonic effects last for around 3 hours *(3)* Half-life: 1–6 minutes (oxytocin) and 30–120 minutes (ergometrine)	See misoprostol and oxytocin

Characteristics	Oxytocin	Carbetocin	Misoprostol	Injectable prostaglandins	Ergometrine	Oxytocin plus ergometrine	Misoprostol plus oxytocin
Storage and transport *(4)*	Requires protection from light, and storage at 2–8 °C[a] to prolong shelf life	A heat-stable formulation of carbetocin[b] is available.	Does not have any special storage requirements. Tablets should be kept in tightly closed containers and protected from humidity.	Requires storage at a temperature between 2 ° and 8 °C[a] to prolong shelf life	Requires protection from light, and storage at a temperature between 2 ° and 8 °C[a] to prolong shelf life	See oxytocin and ergometrine	See misoprostol and oxytocin
WHO Model List of Essential Medicines *(5)*	Listed: 10 IU in 1 ml ampoule for injection	Not listed	Listed: 200 μg tablets[c] and 25 μg tablets	Not listed	Listed: Ergometrine (hydrogen maleate) 200 μg in 1 ml ampoule for injection	Oxytocin and ergometrine are listed separately The fixed-drug combination of oxytocin plus ergometrine (5 IU/500 μg) is not listed.	See misoprostol and oxytocin

IM: intramuscular; IV: intravenous; PPH: postpartum haemorrhage
[a] Due consideration should be given to the manufacturer's instructions on storage and transport.
[b] The heat-stable formulation of carbetocin differs only in its excipients from the existing non-heat-stable formulation.
[c] For the prevention and treatment of PPH where oxytocin is not available or cannot be safely used, and for the management of incomplete abortion and miscarriage.

2. Question

The following is the question of interest in PICO (population, intervention, comparator, outcome) format:

> For women in the third stage of labour (P), is the use of any uterotonic agent(s) (oxytocin, carbetocin, misoprostol, ergometrine/methylergometrine, injectable prostaglandins, oxytocin plus ergometrine, misoprostol plus oxytocin) for prevention of PPH (I) compared with other uterotonic agents (oxytocin, carbetocin, misoprostol, ergometrine/methylergometrine, injectable prostaglandins, oxytocin plus ergometrine, misoprostol plus oxytocin) (C), safer and more effective for improving maternal and perinatal outcomes?
>
> - If so, what route of administration and dosing regimen of such uterotonic agent(s) should be used?

Problem: Preventing the onset of postpartum haemorrhage (PPH)

Perspective: Clinical practice recommendation – population perspective

Population (P): Women in the third stage of labour

Intervention (I): Uterotonic agent (single agent: oxytocin, carbetocin, misoprostol, injectable prostaglandins, ergometrine; or combination agents: oxytocin plus ergometrine, misoprostol plus oxytocin)

Comparator (C): Any uterotonic agent (as above)

Setting: Hospital or community setting[1]

Subgroups: Women undergoing vaginal birth; women undergoing caesarean section

Priority outcomes (O):[2]

- Maternal death
- PPH ≥ 1000 ml
- Blood transfusion
- Severe maternal morbidity: intensive care unit (ICU) admission
- Severe maternal morbidity: shock
- PPH ≥ 500 ml
- Use of additional uterotonics
- Blood loss (ml)
- Postpartum anaemia
- Breastfeeding
- Side-effects[3]
- Maternal well-being
- Maternal satisfaction

[1] For the purposes of the network meta-analysis *(6)*, "community" was defined to include primary health care and home settings or self-administration of a uterotonic by women.

[2] These outcomes reflect the prioritized outcomes used in the development of this recommendation, in the *WHO recommendations for prevention and treatment of postpartum haemorrhage* (2012) *(7)*. The outcomes "shock", "maternal well-being" and "maternal satisfaction" have been added as part of this update.

[3] This includes nausea, vomiting, headache, abdominal pain, hypertension, shivering, fever and diarrhoea.

3. Assessment

3.1 Effects of interventions

What is the effect of uterotonics for PPH prevention on the priority outcomes?

Research evidence

Summary of evidence

Source and characteristics of studies

Evidence on the efficacy and safety of uterotonics for the prevention of postpartum haemorrhage (PPH) was derived from an updated Cochrane systematic review with a network meta-analysis *(6)*. The network meta-analysis included 196 trials (135 559 women) that were conducted across 53 countries (including high-, middle- and low-income countries). Most trials (187/196, 95.4%) were performed in a hospital setting, seven in a community setting (3.6%), one in a mixed setting (0.5%), and in one trial the setting was unclear.

The majority of the trials included women undergoing a vaginal birth (140/196, 71.5%), while 53 trials (27.0%) involved women undergoing caesarean section, two trials (1.0%) included women undergoing either a vaginal birth or caesarean section, and one trial (0.5%) did not specify the mode of birth. A total of 124 trials (63.3%) included women with a singleton pregnancy, 36 trials (18.4%) included women with either singleton or multiple pregnancies, one trial (0.5%) included women with twin pregnancies only and the remaining 35 trials (17.9%) did not specify. A total of 108 trials (55.1%) included both nulliparous and multiparous women, six trials (3.1%) included only nulliparous or primigravida women, one trial included only multiparous women (0.5%), and 81 trials (41.3%) did not specify parity.

Across all 196 trials (412 trial arms) in the network meta-analysis, the following agents were used either as intervention or comparator:

- 137 trial arms (33.3%) used oxytocin
- 96 trial arms (23.3%) used misoprostol
- 39 trial arms (9.5%) used ergometrine
- 35 trial arms (8.5%) used oxytocin plus ergometrine
- 33 trial arms (8%) used carbetocin
- 29 trial arms (7%) used placebo or no treatment
- 26 trial arms (6.3%) used misoprostol plus oxytocin
- 17 trial arms (4.1%) used injectable prostaglandins.

Oxytocin was the reference uterotonic in one third of the trials in the network meta-analysis, and was the most frequently investigated agent across all outcomes. The comparative effects of different uterotonics have therefore been presented using oxytocin as the reference agent.

Effects of uterotonics agents (carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine, misoprostol plus oxytocin) compared with oxytocin (as reference agent)

The results below report the findings of the network meta-analysis for the priority outcomes (which generated effect estimates from both direct and indirect evidence). The findings are summarized in Table 1 below.

Maternal death: See *Summary of Findings table 1*. Pooled effect estimates from the network meta-analysis suggested that there were no meaningful differences between

any of the uterotonic agents versus placebo for maternal death, as this outcome was generally rare. When compared with oxytocin, moderate-certainty evidence suggests that **carbetocin** (relative risk [RR] 2.00, 95% confidence interval [CI] 0.37–10.92) and **misoprostol** (RR 0.62, 95% CI 0.14–2.74) probably make little or no difference to the risk of maternal death. Network relative effects were not estimable for the comparisons of other uterotonics with **oxytocin**.

PPH ≥ 1000 ml: See *Summary of Findings table 2*. None of the agents was found to be more effective when compared with the reference uterotonic agent **oxytocin** for PPH ≥ 1000 ml. High-certainty evidence suggests that **misoprostol plus oxytocin** (RR 0.88, 95% CI 0.70–1.11) and **oxytocin plus ergometrine** (RR 0.83, 95% CI 0.66–1.03) make little or no difference to risk of PPH ≥ 1000 ml when compared with **oxytocin**. Low-certainty evidence suggests that **ergometrine** (RR 0.94, 95% CI 0.48–1.84) may make little or no difference to the risk of this outcome when compared with **oxytocin**. The evidence for **carbetocin** and **injectable prostaglandins** was uncertain. The network evidence shows that **misoprostol** has less protective effect against PPH ≥ 1000 ml when compared with **oxytocin** (high-certainty evidence, RR 1.19, 95% CI 1.01–1.42).

Blood transfusion: See *Summary of Findings table 3*. **Misoprostol plus oxytocin** was the only agent found to be more effective when compared with the reference uterotonic agent **oxytocin** (moderate-certainty evidence, RR 0.52, 95% CI 0.38–0.70).

Severe maternal morbidity – ICU admission: See *Summary of Findings table 4*. Pooled effect estimates for the various comparisons suggested that there were no detectable differences among the uterotonic agents for intensive care unit admission as this outcome was generally rare. When compared with **oxytocin**, moderate-certainty evidence suggests that **carbetocin** (RR 1.16, 95% CI 0.67–2.02) and **misoprostol** (RR 1.16, 95% CI 0.55 to 2.43) probably make little or no difference to the risk of this outcome, while effects are uncertain for **ergometrine**, **oxytocin plus ergometrine** and **misoprostol plus oxytocin** because the certainty of the evidence is very low. This outcome was not reported for any trial involving **injectable prostaglandins**.

PPH ≥ 500 ml: See *Summary of Findings table 5*. When compared with **oxytocin**, moderate-certainty evidence suggests that **carbetocin** (RR 0.72, 95% CI 0.56–0.93) and **oxytocin plus ergometrine** (RR 0.70, 95% CI 0.59–0.84) probably reduce PPH ≥ 500 ml, while low-certainty evidence suggests that **misoprostol plus oxytocin** (RR 0.70, 95% CI 0.58–0.86) may reduce PPH ≥ 500 ml. Low-certainty evidence suggests that **misoprostol**, **injectable prostaglandins** and **ergometrine** may make little or no difference to the risk of this outcome.

Use of additional uterotonics: See *Summary of Findings table 6*. High-certainty evidence suggests that **misoprostol plus oxytocin** (RR 0.57, 95% CI 0.44–0.74) reduces the use of additional uterotonics when compared with **oxytocin**. There is low-certainty evidence that **carbetocin** (RR 0.45, 95% CI 0.34–0.59), **injectable prostaglandins** (RR 0.55, 95% CI 0.31–0.96) and **oxytocin plus ergometrine** (RR 0.66, 95% CI 0.51–0.85) may also reduce the use of additional uterotonics. It is uncertain whether **ergometrine** reduces use of additional uterotonics because the certainty of this evidence is very low.

Mean blood loss: See *Summary of Findings table 7*. When compared with **oxytocin**, moderate-certainty evidence suggests that blood loss is probably on average reduced among women receiving **misoprostol plus oxytocin** (mean difference [MD] 88.31 ml lower, 95% CI 127.08–49.54 ml lower), and that it may be reduced among women receiving **carbetocin** (MD 81.93 ml lower, 95% CI 119.91– 42.87 ml lower). Low-certainty evidence suggests that there may be little or no difference between **ergometrine** (MD 4.82 ml higher, 95% CI 28.00 ml lower to 37.64 ml higher) and **oxytocin** for this outcome. The effects of **misoprostol**, **injectable prostaglandins** and **oxytocin plus ergometrine** is unclear because the certainty of the evidence is very low.

Postpartum anaemia: See *Summary of Findings table 8*. Postpartum anaemia was not directly reported in the review, but there was evidence relating to **mean change in haemoglobin level** before versus after birth. Low-certainty evidence suggests that the mean change in haemoglobin level may be lower among women receiving **misoprostol plus oxytocin** (MD 2.53 g/L lower, 95% CI 3.80 g/L lower to 1.26 g/L lower) and **carbetocin** (MD 2.18 g/L lower, 95% CI from 3.57 g/L lower to 0.79 g/L lower) compared with those receiving **oxytocin**. Low-certainty evidence suggests that there may be little or no difference between **ergometrine** (MD 0.98 g/L higher, 95% CI from 0.74 g/L lower to 2.69 g/L higher) or **oxytocin plus ergometrine** (MD 1.07 g/L lower, 95% CI 2.38 g/L lower to 0.25 g/L higher) and **oxytocin** for this outcome. The effects of **misoprostol** and **injectable prostaglandins** is unclear because the certainty of the evidence is very low.

Breastfeeding: See *Summary of Findings table 9*. High-certainty evidence suggests that **oxytocin plus ergometrine** makes little or no difference to the proportion of women who are breastfeeding at the time of discharge from hospital (RR 0.99, 95% CI 0.96–1.03) when compared with **oxytocin**. There were no clear findings relating to any other uterotonics, either because the evidence was of very low certainty (for **carbetocin**) or the outcome was not reported in any of the included trials (**misoprostol**, **injectable prostaglandins**, **ergometrine**, **misoprostol plus oxytocin**).

Side-effect – nausea: See *Summary of Findings table 10*. Low-certainty evidence suggests that **carbetocin** may make little or no difference to the risk of experiencing of nausea among women when compared with **oxytocin** (RR 1.00, 95% CI 0.71–1.41). However, high-certainty evidence suggests that **oxytocin plus ergometrine** (RR 2.03, 95% CI 1.47–2.79) and **misoprostol plus oxytocin** (RR 1.88, 95% CI 1.14–3.09) combinations increase the risk of nausea compared with **oxytocin**. Moderate-certainty evidence suggests that **misoprostol** (RR 1.41, 95% CI 1.10–1.81), **injectable prostaglandins** (RR 2.25, 95% CI 1.16–4.39), and **ergometrine** (RR 2.40, 95% CI 1.65–3.49) probably increase the risk of nausea compared with **oxytocin**.

Side-effect – vomiting: See *Summary of Findings table 11*. Moderate-certainty evidence suggests that **carbetocin** probably makes little or no difference to the risk of women experiencing vomiting compared with **oxytocin** (RR 0.93, 95% CI 0.64–1.35). When compared with **oxytocin**, high-certainty evidence suggests **misoprostol plus oxytocin** combination (RR 2.11, 95% CI 1.39–3.18) increases the likelihood of vomiting. Moderate-certainty evidence suggests that **oxytocin plus ergometrine** (RR 2.93, 95% CI 2.08–4.13), **misoprostol** (RR 1.63, 95% CI 1.25–2.14) and **ergometrine** (RR 2.36, 95% CI 1.56–3.55) probably increase the likelihood of vomiting, whereas low-certainty evidence suggests that **injectable prostaglandins** (RR 3.76, 95% CI 1.90–7.42) may increase the risk of women experiencing vomiting.

Side-effect – headache: See *Summary of Findings table 12*. When compared with oxytocin, low-certainty evidence suggests that women receiving **ergometrine** (RR 1.89, 95% CI 1.02–3.50) may be more likely to experience headache. Low-certainty evidence also suggests that **carbetocin** (RR 0.94, 95% CI 0.66-1.33), **misoprostol** (RR 0.98, 95% CI 0.69-1.40), and **misoprostol plus oxytocin** (RR 1.48, 95% CI 0.42-5.81) may make little or no difference to the risk of headache when compared with oxytocin. It is uncertain whether **injectable prostaglandins** impact on the risk of women experiencing headache because the certainty of the evidence is very low.

Side-effect – abdominal pain: See *Summary of Findings table 13*. High-certainty evidence suggests that **misoprostol** (RR 1.02, 95% CI 0.80-1.31) and **misoprostol plus oxytocin** (RR 1.93, 95% CI 0.89-4.20) make little or no difference to of the risk of women experiencing abdominal pain when compared with **oxytocin**. Low-certainty evidence suggests that **oxytocin plus ergometrine** (RR 1.39, 95% CI 0.91-2.13) probably make little or no difference to the likelihood of abdominal pain compared with oxytocin. The

effects of **injectable prostaglandins** and **ergometrine** are uncertain as the certainty of the evidence is very low.

Side-effect – hypertension: See *Summary of Findings table 14*. Low-certainty evidence suggests that **ergometrine** (RR 8.54, 95% CI 2.12–34.48) may increase the risk of hypertension when compared with **oxytocin**, whereas **misoprostol** (RR 1.50, 95% 0.49–4.61) and **oxytocin plus ergometrine** (RR 2.48, 95% CI 0.89–6.88) may make little or no difference to the risk of this outcome. It is uncertain whether **carbetocin** or **injectable prostaglandins** increase the risk of hypertension because the certainty of the evidence is very low.

Side-effect – shivering: See *Summary of Findings table 15*. Moderate-certainty evidence suggests that **misoprostol plus oxytocin** (RR 3.62, 95% CI 2.59–5.05) is probably more likely to cause shivering when compared with **oxytocin**. Low-certainty evidence also suggests that **misoprostol** (RR 4.18, 95% CI 3.34–5.23) may increase the likelihood of shivering when compared with **oxytocin**. Moderate-certainty evidence suggests that **oxytocin plus ergometrine** (RR 1.38, 95% CI 0.86–2.22) probably makes little or no difference to the likelihood of shivering when compared with **oxytocin**. Low- certainty evidence suggests that **carbetocin** (RR 0.77, 95% CI 0.46-1.29) and **injectable prostaglandins** (RR 0.50, 95% 0.19-1.31) may make little or no difference to the risk of this outcome when compared with **oxytocin**.

Side-effect – fever: See *Summary of Findings table 16*. Moderate-certainty evidence suggests that **misoprostol** (RR 3.87, 95% CI 2.90–5.16) and **misoprostol plus oxytocin** (RR 3.14, 95% CI 2.20–4.49) probably increase the occurrence of fever when compared with **oxytocin**. Moderate-certainty evidence suggests that **carbetocin** (RR 1.07, 95% CI 0.43–2.69) probably makes little or no difference to the likelihood of fever. Low-certainty evidence suggests that **injectable prostaglandins** (RR 1.12, 95% CI 0.33–3.86) and **oxytocin plus ergometrine** (RR 0.70, 95% CI 0.35–1.42) may make little or no difference to the risk of this outcome when compared with **oxytocin**. The comparative effect of **ergometrine** on this outcome is uncertain because the certainty of the evidence is very low.

Side-effect – diarrhoea: See *Summary of Findings table 17*. High-certainty evidence shows that **misoprostol** (RR 2.24, 95% CI 1.64–3.05) and **misoprostol plus oxytocin** (RR 1.82, 95% CI 1.12–2.98) increase the likelihood of diarrhoea when compared with **oxytocin**. Moderate-certainty evidence suggests that **oxytocin plus ergometrine** (RR 1.80, 95% CI 1.18–2.75) and **injectable prostaglandins** (RR 23.41, 95% CI 11.03–49.70) probably increase the likelihood of diarrhoea when compared with **oxytocin**. Low-certainty evidence suggests that women receiving **ergometrine** (RR 2.51, 95% CI 1.20–5.26) may experience diarrhoea more frequently compared with women receiving **oxytocin**.

Table 1. Summary of treatment effects of uterotonic agents versus reference agent (oxytocin) on beneficial outcomes

Desirable outcomes	Oxytocin (absolute risk)	Carbetocin	Misoprostol	Injectable prosta-glandins	Ergometrine	Oxytocin plus ergometrine	Misoprostol plus oxytocin
Maternal death	1 per 1000	Probably similar effect	Probably similar effect	Don't know	Don't know	Don't know	Don't know
PPH ≥ 1000 ml	37 per 1000	Uncertain	Inferior	Uncertain	Possibly similar effect	Similar effect	Similar effect
Blood transfusion	22 per 1000	Probably similar effect	Probably similar effect	Uncertain	Possibly similar effect	Possibly similar effect	Probably superior
ICU admissions	2 per 1000	Probably similar effect	Probably similar effect	Don't know	Uncertain	Uncertain	Uncertain
PPH ≥ 500 ml	145 per 1000	Probably superior	Possibly similar effect	Possibly similar effect	Possibly similar effect	Probably superior	Possibly superior
Additional uterotonics	135 per 1000	Possibly superior	Possibly similar effect	Possibly superior	Uncertain	Possibly superior	Probably superior
Blood loss	301.5 ml (98–1299 ml)	Possibly superior	Uncertain	Uncertain	Possibly similar effect	Uncertain	Probably superior
Change in haemoglobin	11.37 g/L (2.30–27.9 g/L)	Possibly superior	Uncertain	Uncertain	Possibly similar effect	Possibly similar effect	Possibly superior
Breastfeeding	849 per 1000	Uncertain	Don't know	Don't know	Don't know	Similar effect	Don't know

ICU: intensive care unit; PPH: postpartum haemorrhage
Superior, inferior or similar effect: high-certainty evidence of different effect or no effect
Probably superior, probably inferior or probably similar effect: moderate-certainty evidence of different effect or no effect
Possibly superior, possibly inferior or possibly similar effect: low-certainty evidence of different effect or no effect
Uncertain: very low-certainty evidence (regardless of effect)
Don't know: outcome not reported/not estimable.

Additional considerations

Subgroup analyses did not reveal a substantial difference by mode of birth (vaginal versus caesarean section) or setting (community versus hospital) in the effects of uterotonic agents on the above outcomes when compared with oxytocin as the reference uterotonic agent.

Desirable effects

How substantial are the desirable anticipated effects of different uterotonics (carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine, and misoprostol plus oxytocin) compared with oxytocin (as the reference agent)?

Judgement

Carbetocin	— Don't know	— None	— Trivial	✓ Small	— Moderate	— Large
Misoprostol	— Don't know	✓ None	— Trivial	— Small	— Moderate	— Large
Injectable prostaglandins	— Don't know	✓ None	— Trivial	— Small	— Moderate	— Large
Ergometrine	— Don't know	✓ None	— Trivial	— Small	— Moderate	— Large
Oxytocin plus ergometrine	— Don't know	— None	— Trivial	✓ Small	— Moderate	— Large
Misoprostol plus oxytocin	— Don't know	— None	— Trivial	— Small	✓ Moderate	— Large

Undesirable effects

How substantial are the undesirable anticipated effects of different uterotonics (carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine, and misoprostol plus oxytocin) compared with oxytocin (as the reference agent)?

Judgement

Carbetocin	— Don't know	— Large	— Moderate	— Small	— Trivial	✓ None
Misoprostol	— Don't know	— Large	✓ Moderate	— Small	— Trivial	— None
Injectable prostaglandins	— Don't know	— Large	✓ Moderate	— Small	— Trivial	— None
Ergometrine	— Don't know	— Large	✓ Moderate	— Small	— Trivial	— None
Oxytocin plus ergometrine	— Don't know	— Large	✓ Moderate	— Small	— Trivial	— None
Misoprostol plus oxytocin	— Don't know	✓ Large	— Moderate	— Small	— Trivial	— None

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Certainty of the evidence

What is the overall certainty of the evidence of effects of different uterotonics (carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine, and misoprostol plus oxytocin) compared with oxytocin (as the reference agent)?

Carbetocin	— No included studies	— Very low	— Low	✓ Moderate	— High
Misoprostol	— No included studies	— Very low	— Low	✓ Moderate	— High
Injectable prostaglandins	— No included studies	✓ Very low	— Low	— Moderate	— High
Ergometrine	— No included studies	— Very low	✓ Low	— Moderate	— High
Oxytocin plus ergometrine	— No included studies	— Very low	— Low	✓ Moderate	— High
Misoprostol plus oxytocin	— No included studies	— Very low	— Low	✓ Moderate	— High

Additional considerations

None.

3.2 Values

Is there important uncertainty about, or variability in, how much women (and their families) value the main outcomes associated with different uterotonics (oxytocin, carbetocin, misoprostol, injectable prostaglandins, ergometrine, ergometrine plus oxytocin and misoprostol plus oxytocin) for PPH prevention?

Research evidence

In a review of qualitative studies looking at "what women want" from intrapartum care, findings indicate that most women want a normal birth (with good outcomes for mother and baby), but acknowledge that medical intervention may sometimes be necessary *(high confidence) (8)*. Most women, especially those giving birth for the first time, are apprehensive about labour and birth *(high confidence)* and wary of medical interventions, although in certain contexts and/or situations women welcome interventions to address recognized complications *(low confidence)*. Where interventions are introduced, women would like to receive relevant information from technically competent health care providers who are sensitive to their needs *(high confidence)*.

Findings from another qualitative systematic review exploring perceptions of PPH prevention and treatment among women and providers suggest that women do not recognize the clinical definitions of blood loss or what might be considered "normal" blood loss *(moderate confidence) (9)*. Furthermore, in some low- and middle-income countries (LMICs), women place a greater value on the expulsion of so-called "dirty

blood", which they perceive as a normal cleansing process and something that should not be prevented *(moderate confidence)*.

The same review highlighted women's need for information about PPH, ideally given during antenatal care *(moderate confidence)*, and the importance of kind, clinically competent staff with a willingness to engage in shared decision-making around PPH management *(moderate/low confidence)*. In addition, it was found that women are concerned about feelings of exhaustion and anxiety (at being separated from their baby) following PPH, as well as the long-term psychological effects of experiencing PPH and the negative impact this may have on their ability to breastfeed *(moderate/low confidence)*.

Additional considerations

Women typically place a higher value on avoiding severe adverse effects resulting from PPH (death, severe blood loss, blood transfusion) compared with avoiding side-effects of uterotonics, which in some instances are self-limiting. There is probably no important variability in how much value women place on avoiding the severe complications across settings, irrespective of the uterotonic agents being considered.

Judgement

—	—	✓	—
Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability

Balance of effects

Does the balance between desirable and undesirable effects favour different uterotonics (carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine, and misoprostol plus oxytocin) or oxytocin (the reference agent)?

Judgement

Carbetocin	— Don't know	— Varies	— Favours oxytocin	— Probably favours oxytocin	— Does not favour either	✓ Probably favours carbetocin	— Favours carbetocin
Misoprostol	— Don't know	— Varies	✓ Favours oxytocin	— Probably favours oxytocin	— Does not favour either	— Probably favours misoprostol	— Favours misoprostol
Injectable prostaglandins	— Don't know	— Varies	✓ Favours oxytocin	— Probably favours oxytocin	— Does not favour either	— Probably favours injectable prostaglandins	— Favours injectable prostaglandins
Ergometrine	— Don't know	— Varies	— Favours oxytocin	✓ Probably favours oxytocin	— Does not favour either	— Probably favours ergometrine	— Favours ergometrine
Oxytocin plus ergometrine	— Don't know	— Varies	✓ Favours oxytocin	— Probably favours oxytocin	— Does not favour either	— Probably favours ergometrine plus oxytocin	— Favours ergometrine plus oxytocin
Misoprostol plus oxytocin	— Don't know	— Varies	✓ Favours oxytocin	— Probably favours oxytocin	— Does not favour either	— Probably favours misoprostol plus oxytocin	— Favours misoprostol plus oxytocin

3.3 Resources

How large are the resource requirements (costs) of different uterotonics (carbetocin, misoprostol, injectable prostaglandins, ergometrine, ergometrine plus oxytocin and misoprostol plus oxytocin) compared with oxytocin (the reference agent) for PPH prevention?

Research evidence

An economic assessment was conducted to assess the cost consequences of various single or combination uterotonic agents compared with oxytocin, with consideration of differences between their effects (benefits and harms), supply costs and other resource requirements (staffing and training, equipment and infrastructure, staff time, supplies, and supervision and monitoring) *(10)*. The period of interest was the immediate postpartum period. Table 2 summarizes:

- network evidence on the effects (benefits and harms) of uterotonic agents relative to oxytocin (superior, inferior, similar, uncertain), derived from an update of a Cochrane systematic review and network meta-analysis on uterotonics for PPH prevention (as presented above) *(11)*;
- supply costs of uterotonic agents in one high-income country were obtained as an example of relative costs from a setting (the United Kingdom of Great Britain and Northern Ireland) where all of the uterotonic agents under consideration were available *(12)*;
- implications of the different uterotonic agents on resource requirements relative to oxytocin (10 IU intramuscular injection).

- **Carbetocin versus oxytocin:** The supply cost of carbetocin is approximately 20 times more than that of oxytocin. Evidence on effects suggests that for most priority outcomes, its effects are similar or possibly superior to those of oxytocin. However, due to evidence suggesting a reduction in the use of additional uterotonics with carbetocin by about half, there might be cost savings related to that outcome. Unlike oxytocin, carbetocin does not require cold chain storage although this translates to negligible cost saving as the cost of maintaining cold chain is almost equivalent to oxytocin supply cost. However, if the supply cost of carbetocin becomes comparable to that of oxytocin (as indicated in the memorandum of understanding signed between WHO and manufacturer of a heat-stable formulation of carbetocin *[13]*), then moderate to large cost savings can be expected in the longer term given that other resource requirements (e.g. staff and supplies) are similar between carbetocin and oxytocin.
- **Misoprostol versus oxytocin:** The supply cost of misoprostol is approximately 0.56 times that of oxytocin. Evidence on relative effects suggests that it is less effective than oxytocin at reducing severe PPH and use of additional uterotonics but it is probably similar for other priority outcomes. There might be costs associated with managing side-effects of misoprostol (shivering, fever, vomiting and diarrhoea), which are likely to vary according to the setting depending on factors such as bed costs and approach to managing these side-effects. Unlike oxytocin, misoprostol does not require cold chain storage, which might represent a cost saving, and it also has the potential for other cost-savings due to its oral route of administration (easier administration, no additional supplies necessary, and can be task shifted).
- **Injectable prostaglandins (carboprost) versus oxytocin:** The supply cost of carboprost is approximately 20 times more than that of oxytocin. There is insufficient evidence of its effectiveness compared with oxytocin and resource requirements would depend on the extent to which it is necessary for staff to manage the associated side-effects (vomiting and diarrhoea).

- **Ergometrine versus oxytocin:** The supply cost of ergometrine is approximately 1.7 times that of oxytocin. Ergometrine is possibly inferior to oxytocin for several priority outcomes, and there are likely to be higher resource requirements associated with a need for staff to monitor for and manage its side-effects (vomiting, diarrhoea, hypertension and headache).
- **Oxytocin plus ergometrine versus oxytocin:** The supply cost of oxytocin plus ergometrine is approximately 1.7 times that of oxytocin. Evidence on effects suggests that for most priority outcomes its effects are similar to oxytocin. However, due to evidence suggesting a reduction in the use of additional uterotonics by about a third, there might be cost savings, depending on the extent to which it is necessary for staff to manage its side-effects (vomiting, diarrhoea and, possibly, hypertension).
- **Misoprostol plus oxytocin versus oxytocin:** The supply cost of misoprostol plus oxytocin is approximately 1.4 times that of oxytocin. Evidence on effects suggests that, compared with oxytocin, the combination of misoprostol plus oxytocin might be associated with cost savings due to a reduced need for blood transfusions and additional uterotonic agents. However, there might be costs associated with managing side-effects of misoprostol (shivering, fever, vomiting and diarrhoea), which are likely to vary according to the setting depending on factors such as bed costs and approach to managing these side-effects.

Additional considerations

None.

Table 2. Relative effects and resource implications of different uterotonic agents compared with oxytocin

	Oxytocin (10 IU)	Carbetocin (100 μg)	Misoprostol (600 μg)	Injectable prostaglandin: carboprost (250 μg)	Ergometrine (500 μg)	Oxytocin (5 IU) plus ergometrine (500 μg)	Misoprostol (400 μg) plus oxytocin (10 IU)
Indicative uterotonic agent costs *(12)*							
£	0.90	17.64	0.50	18.20	1.50	1.51	1.22
US$ equivalent[a]	1.18	23.11[b]	0.66	23.84	1.97	1.98	1.60
Relative cost compared with oxytocin (10 IU)[c]	1	19.60[d]	0.56	20.22	1.67	1.68	1.36
Relative risks of desirable effects (in terms of reduction)							
PPH ≥ 1000 ml	1	0.87 (0.62–1.21)	1.19 (1.01–1.42)	0.88 (0.41–1.89)	0.94 (0.48–1.84)	0.83 (0.66–1.03)	0.88 (0.70–1.11)
Blood transfusion	1	0.81 (0.49–1.32)	0.88 (0.68–1.13)	0.66 (0.25–1.72)	1.11 (0.54–2.28)	0.78 (0.59–1.03)	0.52 (0.38–0.70)
Additional uterotonics	1	0.45 (0.34–0.59)	1.04 (0.88–1.24)	0.55 (0.31–0.96)	0.97 (0.69–1.36)	0.66 (0.51–0.85)	0.57 (0.44–0.74)
PPH ≥ 500 ml	1	0.72 (0.56–0.93)	1.08 (0.97–1.22)	1.05 (0.73–1.51)	1.09 (0.85 –1.39)	0.70 (0.59–0.84)	0.70 (0.58–0.86)
Maternal death	1	2.00 (0.37 – 10.92)	0.62 (0.14–2.74)	No estimate	No estimate	No estimate	No estimate
ICU admissions	1	1.16 (0.67–2.02)	1.16 (0.55–2.43)	No estimate	0.39 (0.01–10.27)	2.99 (0.12–73.32)	0.50 (0.05–5.47)
Relative risks of undesirable effects							
Shivering	1	0.77 (0.46–1.29)	4.18 (3.34–5.23)	0.50 (0.19–1.31)	1.31 (0.86–1.99)	1.38 (0.86–2.22)	3.62 (2.59–5.05)
Fever	1	1.07 (0.43–2.69)	3.87 (2.90–5.16)	1.12 (0.33–3.86)	0.77 (0.44–1.35)	0.70 (0.35–1.42)	3.14 (2.20–4.49)
Nausea	1	1.00 (0.71 – 1.41)	1.41 (1.10 – 1.81)	2.25 (1.16 – 4.39)	2.40 (1.65 – 3.49)	2.03 (1.47 – 2.79)	1.88 (1.14 – 3.09)
Vomiting	1	0.93 (0.64–1.35)	1.63 (1.25–2.14)	3.76 (1.90–7.41)	2.36 (1.56–3.55)	2.93 (2.08–4.13)	2.11 (1.39–3.18)
Diarrhoea	1	No estimate	2.24 (1.64–3.05)	23.41 (11.03–49.7)	2.51 (1.20–5.26)	1.80 (1.18–2.75)	1.82 (1.12–2.98)

	Oxytocin (10 IU)	Carbetocin (100 μg)	Misoprostol (600 μg)	Injectable prostaglandin: carboprost (250 μg)	Ergometrine (500 μg)	Oxytocin (5 IU) plus ergometrine (500 μg)	Misoprostol (400 μg) plus oxytocin (10 IU)
Hypertension	1	1.24 (0.28–5.56)	1.50 (0.49–4.61)	1.40 (0.09–20.66)	8.54 (2.12–34.48)	2.48 (0.89–6.88)	No estimate
Abdominal pain	1	1.13 (0.90–1.44)	1.02 (0.80–1.31)	1.41 (0.39–5.09)	2.13 (0.98–4.62)	1.39 (0.91–2.13)	1.93 (0.89–4.20)
Headache	1	0.94 (0.66–1.33)	0.98 (0.69–1.40)	1.76 (0.33–9.31)	1.89 (1.02–3.50)	1.08 (0.73–1.61)	1.48 (0.42–5.81)
Other resource requirements relative to oxytocin							
Staff and training	Trained maternity staff	Same as for oxytocin	Trained lay health workers can also administer	Same as for oxytocin	Same as for oxytocin	Same as for oxytocin	Same as for oxytocin[e]
Supplies	Needle, syringe and swab US$0.07 *(14)*	Same as for oxytocin	No needle, syringe and swab needed	Same as for oxytocin	Same as for oxytocin	Same as for oxytocin	Same as for oxytocin
Equipment and infrastructure	Cold chain storage[f] *(15)*; hazardous waste disposal	Heat stable; also requires hazardous waste disposal	Heat stable	Same as for oxytocin	Same as for oxytocin	Same as for oxytocin	Same as for oxytocin
Staff time	2 minutes to administer *(16)*; time needed for managing side-effects is minimal	Same as for oxytocin	Less time to administer, but possibly more staff time managing side-effects	Possibly more staff time to manage side-effects	More staff time to manage side-effects	Possibly more staff time to manage side-effects	Same as for oxytocin
Supervision and monitoring	Cold chain requires monitoring of stock quality	Possibly more staff time (if not used previously)	Possibly more staff time to manage side-effects	Possibly more staff time to manage side-effects	More staff time to manage side-effects	Possibly more staff time to manage side-effects	Possibly more staff time to manage side-effects

ICU: intensive care unit
Relative risks are given with their 95 per cent confidence intervals in brackets
Green: superior effect or fewer resource requirements
Red: inferior effect or more resource requirements
Grey: similar effect (or slightly better or slightly worse point estimate, defined as a confidence interval (CI) range of less than or equal to 100 points) or comparable resource requirements
White: unknown, uncertain or any effect possible due to wide CI that includes the point estimate of 1, or resource requirements are not known or vary.

[a] Converted using a ratio of US$ 1.31 : £1 (rate on 22 August 2018).
[b] The manufacturer of heat-stable carbetocin has committed to seeking registration and to manufacture heat-stable carbetocin for the public sector in low- and lower-middle income countries at an affordable and sustainable price *(13)*, which is a subsidized price of US$ 0.31 +/–10% per ampoule of 100 μg. The price set by the United Nations Population Fund (UNFPA) (12 September 2018) of oxytocin is US$ 0.27 per unit (10 IU).
[c] The cost of the drug divided by the cost of oxytocin (10 IU) (both in £).
[d] Relative cost of carbetocin (at the subsidized price of US$ 0.31 +/- 10%) compared with oxytocin (USD $ 0.27) is 1.03 to 1.26.
[e] Oxytocin administered from a Uniject device could be administered by trained lay health workers. This form of oxytocin might have required fewer staff resources than other injectable uterotonics. This device has been discontinued.
[f] The cost of this resource has been estimated in one study as US$ 0.84 per birth in a low-resource setting *(17)*.

Resources required

Judgement

Carbetocin	— Varies	— Large costs	✓ Moderate costs	— Negligible costs or savings	— Moderate savings	— Large savings
Misoprostol	✓ Varies	— Large costs	— Moderate costs	— Negligible costs or savings	— Moderate savings	— Large savings
Injectable prostaglandins	— Varies	✓ Large costs	— Moderate costs	— Negligible costs or savings	— Moderate savings	— Large savings
Ergometrine	— Varies	— Large costs	✓ Moderate costs	— Negligible costs or savings	— Moderate savings	— Large savings
Oxytocin plus ergometrine	— Varies	— Large costs	— Moderate costs	✓ Negligible costs or savings	— Moderate savings	— Large savings
Misoprostol plus oxytocin	✓ Varies	— Large costs	— Moderate costs	— Negligible costs or savings	— Moderate savings	— Large savings

Certainty of the evidence on required resources

What is the certainty of the evidence on costs?

Carbetocin	— No included studies	— Very low	✓ Low	— Moderate	— High
Misoprostol	— No included studies	— Very low	✓ Low	— Moderate	— High
Injectable prostaglandins	— No included studies	— Very low	✓ Low	— Moderate	— High
Ergometrine	— No included studies	— Very low	✓ Low	— Moderate	— High
Oxytocin plus ergometrine	— No included studies	— Very low	✓ Low	— Moderate	— High
Misoprostol plus oxytocin	— No included studies	— Very low	✓ Low	— Moderate	— High
Oxytocin	— No included studies	— Very low	✓ Low	— Moderate	— High

Cost-effectiveness

Does the cost-effectiveness of the following uterotonics favour the uterotonic or oxytocin?

Judgement

Carbetocin	— Don't know	— Varies	— Favours oxytocin	✓ Probably favours oxytocin	— Does not favour either	— Probably favours carbetocin	— Favours carbetocin
Misoprostol	— Don't know	✓ Varies	— Favours oxytocin	— Probably favours oxytocin	— Does not favour either	— Probably favours misoprostol	— Favours misoprostol
Injectable prostaglandins	— Don't know	— Varies	✓ Favours oxytocin	— Probably favours oxytocin	— Does not favour either	— Probably favours injectable prostaglandins	— Favours injectable prostaglandins
Ergometrine	— Don't know	— Varies	✓ Favours oxytocin	— Probably favours oxytocin	— Does not favour either	— Probably favours ergometrine	— Favours ergometrine
Oxytocin plus ergometrine	— Don't know	— Varies	— Favours oxytocin	✓ Probably favours oxytocin	— Does not favour either	— Probably favours ergometrine plus oxytocin	— Favours ergometrine plus oxytocin
Misoprostol plus oxytocin	— Don't know	✓ Varies	— Favours oxytocin	— Probably favours oxytocin	— Does not favour either	— Probably favours misoprostol plus oxytocin	— Favours misoprostol plus oxytocin

3.4 Equity

What would be the impact of the use of the uterotonics **carbetocin**, **misoprostol**, **injectable prostaglandins**, **ergometrine**, **oxytocin plus ergometrine** and **misoprostol plus oxytocin** compared with **oxytocin** for PPH prevention on health equity?

Research evidence

No direct evidence regarding impacts on health equity for comparisons of different uterotonics was identified.

Findings from a qualitative systematic review exploring perceptions of PPH prevention and treatment by women and health care providers showed that some uterotonics (such as **oxytocin**, **misoprostol** and **ergometrine**) are relatively inexpensive and already widely available in a range of resource settings *(9)*. However, inconsistent stock levels and/or heat sensitivity of some uterotonics (such as for **oxytocin**, **ergometrine** or any combination that included either **oxytocin** or **ergometrine**) may limit their use in low-resource settings in LMICs, particularly in isolated rural areas where the need is arguably greatest *(moderate confidence)*. In some contexts (India and Sierra Leone), supply issues have resulted in women and health care professionals turning to private suppliers to purchase uterotonics, at additional cost to themselves, in order to fulfil guideline recommendations. Advanced distribution of **misoprostol** to women in low-resource rural communities may be a useful approach in reducing maternal mortality (as a consequence of PPH) for women who may not routinely present to a health care facility to give birth *(moderate confidence)*. There was no direct evidence on the differential impact of introducing **carbetocin**, **injectable prostaglandins** or **ergometrine** compared with **oxytocin** or other uterotonics for PPH prevention on health equity.

Additional considerations

The 2015 WHO *State of inequality* report indicates that women who are poor, least educated, and who reside in rural areas have lower health intervention coverage and worse health outcomes than more advantaged women *(18)*. Reducing priority outcomes related to blood loss (such as the effects identified for **oxytocin**, **carbetocin**, **misoprostol**, **ergometrine**, **oxytocin plus ergometrine** and **misoprostol plus oxytocin**) could have a positive impact on health equity and improve outcomes among disadvantaged women. However, there is insufficient evidence on the effects of **injectable prostaglandins** (**carboprost** and **sulprostone**) for most priority outcomes, and they cause undesirable side-effects (especially diarrhoea), and thus may not have an impact on health equity. There was a reduced need for additional interventions to treat PPH (such as reduced use of additional uterotonics and reduced blood transfusion) for **oxytocin**, **carbetocin**, **misoprostol**, **oxytocin plus ergometrine** and **misoprostol plus oxytocin**. These benefits would probably reduce health inequities, especially in contexts where health services are covered through out-of-pocket means.

The price of **carbetocin** and **injectable prostaglandins** (specifically **carboprost**) may make these options unaffordable for health services where resources are limited (e.g. where maintenance of cold storage for **oxytocin** is a challenge), and/or where women are required to pay for health services out of pocket. However, the heat stability potential of **carbetocin** eliminates the need to cold chain storage and transport and reduces wastage that could be associated with temperature-unstable uterotonics.

In low-resource settings where the incidence of pre-eclampsia/eclampsia is relatively high, the routine administration of **ergometrine** or **oxytocin plus ergometrine** may present difficulties given the limited capacity and capability to routinely screening for hypertensive disorders of pregnancy before their administration.

Judgement[1]

Carbetocin	— Don't know	✓ Varies	— Reduced	— Probably reduced	— Probably no impact	— Probably increased	— Increased
Misoprostol	— Don't know	— Varies	— Reduced	— Probably reduced	— Probably no impact	✓ Probably increased	— Increased
Injectable prostaglandins	— Don't know	— Varies	✓ Reduced	— Probably reduced	— Probably no impact	— Probably increased	— Increased
Ergometrine	— Don't know	— Varies	— Reduced	✓ Probably reduced	— Probably no impact	— Probably increased	— Increased
Oxytocin plus ergometrine	— Don't know	— Varies	— Reduced	✓ Probably reduced	— Probably no impact	— Probably increased	— Increased
Misoprostol plus oxytocin	— Don't know	— Varies	— Reduced	— Probably reduced	— Probably no impact	✓ Probably increased	— Increased
Oxytocin	— Don't know	— Varies	— Reduced	— Probably reduced	— Probably no impact	✓ Probably increased	— Increased

[1] These judgements reflect the judgements from Evidence to Decision frameworks comparing each uterotonic to placebo / no treatment for effects on health equity.

3.5 Acceptability

Are different uterotonics (**carbetocin**, **misoprostol**, **injectable prostaglandins**, **ergometrine, oxytocin plus ergometrine**, **misoprostol plus oxytocin**, and **oxytocin**) for PPH prevention acceptable to key stakeholders?

Research evidence

Findings from a qualitative systematic review exploring perceptions of PPH prevention and treatment by women and health care providers suggest that providers would use a uterotonic to prevent PPH if it was shown to be effective *(moderate confidence) (9)*. In certain LMIC settings, traditional birth attendants (TBAs) prefer to use herbal medicines with uterotonic properties *(moderate confidence)*, while in several high-income countries, experienced midwives use expectant management techniques and make selective use of guideline recommendations (ignoring uterotonics use), especially if the birth is perceived to be normal *(moderate confidence) (9)*.

The qualitative review identified that providers recognize the benefits of using **oxytocin** to prevent PPH and hasten the delivery of the placenta *(moderate confidence) (9)*. However, in some LMIC settings, providers hold the perception that **oxytocin** may cause retained placenta when administered preventatively or even contribute to PPH when given to induce labour *(moderate confidence) (9)*.

Providers also recognized the benefits of using **misoprostol** to prevent PPH, especially in rural areas of LMICs where community-based distribution programmes are in place. In these contexts, **misoprostol** was perceived to be safe, effective and more practical to use compared with **oxytocin** *(low confidence)*. However, government officials and regional health care managers in some LMICs had concerns about the influence of civil society organizations (CSOs), nongovernmental organizations (NGOs) and private providers in "pushing" **misoprostol** for other conditions (treatment of PPH) contrary to national guidelines *(moderate confidence)*. In some LMICs, providers (including government officials, health care managers and health care professionals) had concerns about the potential mis-use of **misoprostol** in community contexts where it might be used to induce abortion or act as a deterrent to facility-based deliveries *(moderate confidence)*. In addition, a number of providers, largely based in LMICs, felt they needed more information on the effectiveness of **misoprostol** and further guidance on successful implementation strategies for community distribution in LMICs *(moderate confidence)*. One study in Indonesia highlighted shivering as a potential concern for some women taking **misoprostol** tablets *(moderate confidence)*. No direct evidence was found regarding acceptability of **carbetocin** and **injectable prostaglandins**, which are generally not available in lower-resource settings.

There were no direct findings from studies of women's perspectives relating to the acceptability of uterotonic options.

Additional considerations

In a survey-based evaluation of Uniject devices prefilled with 10 IU of **oxytocin**, conducted in Mali, a variety of providers found the device easier to use compared with **oxytocin** delivered via a standard syringe (99.3%; 139/140), with similar reductions in PPH and retained placenta *(19)*. The authors concluded that "the evaluation demonstrated high levels of acceptability of the oxytocin-Uniject device and relative ease of training health care providers in its use, meaning that its introduction for use by most cadres should be relatively easy".

A number of survey-based studies were identified that looked at the potential benefits of advanced **misoprostol** distribution in rural settings of LMICs where the maternal mortality ratio was relatively high (20–34). The studies were conducted in Afghanistan, Bangladesh, Ethiopia (two studies), Ghana, Liberia, Madagascar, Mozambique, Nepal, Nigeria (three studies), Pakistan (two studies), South Sudan and the United Republic of Tanzania. In most instances, **misoprostol** tablets were given to trained community health workers, community health volunteers or traditional birth attendants who then supplied the tablets (usually 3 x 200 μg tablets) to pregnant women in community settings via a home visit or at an antenatal appointment during the eighth month of pregnancy. During the home visit or appointment women were also given information on PPH, the nature of the **misoprostol** tablets and how/when to take them, as well as details of potential side-effects. Nearly all of the studies reported high levels of usage, acceptability and coverage, with very few safety concerns. One study from Liberia found that 87/265 (32.8%) of women took the **misoprostol** tablets after the delivery of the placenta but experienced few or no ill effects from doing so *(31)*.

A recent qualitative study was undertaken in Ethiopia, India and Myanmar with 158 health care providers (pharmacists, midwives, nurses, doctors and obstetricians) and 40 key informants (supply chain experts, programme managers and policy-makers) *(35)*. It included direct observations of **oxytocin** storage practices and cold chain resources in 51 health care facilities. Many respondents in Ethiopia were aware of **oxytocin**'s heat sensitivity and the requirement for cold storage, but this was less common among participants in India and Myanmar. Maintaining a consistent cold chain was hampered by lack of refrigeration facilities and unreliability of electricity. Poor-quality **oxytocin** supply was evident in a study undertaken in the Democratic Republic of the Congo where some stakeholders believed that the quality of available **oxytocin** was compromised *(36)*. **Oxytocin** ampoules were sampled from 15 facilities (public and private, urban and rural) in five Democratic Republic of the Congo provinces: 80% of ampoules contained less than 90% of the specified content. The authors concluded that "there is evidence of a high prevalence of poor quality oxytocin ampoules in health facilities in the DRC likely resulting from both manufacturing quality issues and uncontrolled storage".

Judgement[1]

Carbetocin	— Don't know	✓ Varies	— No	— Probably No	— Probably Yes	— Yes
Misoprostol	— Don't know	— Varies	— No	— Probably No	✓ Probably Yes	— Yes
Injectable uterotonics	✓ Don't know	— Varies	— No	— Probably No	— Probably Yes	— Yes
Ergometrine	— Don't know	— Varies	— No	— Probably No	✓ Probably Yes	— Yes
Oxytocin plus ergometrine	— Don't know	— Varies	— No	— Probably No	✓ Probably Yes	— Yes
Misoprostol plus oxytocin	— Don't know	— Varies	— No	— Probably No	✓ Probably Yes	— Yes
Oxytocin	— Don't know	✓ Varies	— No	— Probably No	— Probably Yes	— Yes

3.6 Feasibility

Are different uterotonics (**oxytocin**, **carbetocin**, **misoprostol**, **injectable prostaglandins**, **ergometrine**, **oxytocin plus ergometrine**, **misoprostol plus oxytocin** and **oxytocin**) feasible to implement for PPH prevention?

Research evidence

Findings from a qualitative systematic review exploring perceptions of PPH prevention and treatment by women and providers indicate that resource constraints may influence the use of a uterotonic for PPH prevention, particularly in LMICs *(high confidence) (9)*. In a wide variety of settings, health care providers feel they do not have sufficient staff with experience of using uterotonics *(high confidence)* and need more training in PPH management *(high confidence)*. Inconsistent supplies and reservations about **oxytocin** storage in areas with limited/inconsistent electricity hinder utilization, and a lack of experienced staff to administer the injection limits use in certain contexts *(high confidence)*.

In some areas where task shifting had been introduced to address staff shortages, health care professionals were occasionally suspicious about the ability of TBAs or community health workers to administer **oxytocin** correctly. There was a perception in some settings that TBAs and community health workers were poorly trained and untrustworthy *(moderate confidence)*, though TBAs felt they were competent enough and rarely had to deal with a PPH *(moderate confidence)*.

There were no findings from the reviewed studies on women's perceptions relating to the feasibility of any of the uterotonic options.

[1] These judgements reflect the judgements from Evidence to Decision frameworks comparing each uterotonic to placebo/no treatment for acceptability to stakeholders.

Williams MJ, *et al. BMJ Glob Health* 2023; 8:e013109. doi: 10.1136/bmjgh-2023-013109

Additional considerations

The feasibility of using a uterotonic is directly affected by its local availability. **Oxytocin** (10 IU in 1 ml for injection), **misoprostol** (200 μg tablet) and **ergometrine** (200 μg in 1 ml ampoule for injection) are listed on the WHO Model List of Essential Medicines *(5)*, are widely available in a range of resource settings, and have multiple applications in reproductive health. Other uterotonics (including the fixed-dose **oxytocin plus ergometrine** combination) are not listed. **Ergometrine** is contraindicated in severe hypertension and eclampsia, as there is a risk of hypertension associated with its use. The need to exclude hypertensive disorders of pregnancy may affect feasibility, particularly where trained health care providers are scarce.

The qualitative systematic review found that **oxytocin** storage in areas with limited/inconsistent electricity may hinder utilization *(high confidence)*. A recent qualitative study undertaken in Ethiopia, India and Myanmar with 158 health care providers (pharmacists, midwives, nurses, doctors and obstetricians) and 40 key informants (supply chain experts, programme managers and policy-makers) *(35)*. It included direct observations of **oxytocin** storage practices and cold chain resources in 51 health care facilities. Many respondents in Ethiopia were aware of **oxytocin**'s heat sensitivity and the requirement for cold storage, but this was less common among participants in Myanmar and India. Maintaining a consistent cold chain was hampered by lack of refrigeration facilities and unreliability of electricity. A study undertaken in the Democratic Republic of the Congo sampled **oxytocin** injection ampoules from 15 facilities (public and private, urban and rural) across five provinces, using overt sampling and "mystery shopper" approaches. Eighty percent of ampoules collected contained less than 90% of the specified content. The authors concluded that "there is evidence of a high prevalence of poor quality oxytocin ampoules in health facilities in the DRC likely resulting from both manufacturing quality issues and uncontrolled storage" *(37)*.

The heat-stable formulation of **carbetocin** does not require cold chain transport and refrigerated storage, and thus may be more feasible. In a survey-based evaluation of Uniject devices prefilled with 10 IU of **oxytocin**, conducted in Mali, the authors noted that the devices came with a "TempTime Indicator" (TTI) which changed colour following prolonged exposure to heat *(19)*. Of 15 000 devices distributed in rural Mali, only 1 of the 30 health centres visited had 10 devices or more that were heat expired. Most devices were stored in refrigerators or portable cool boxes – 19.0% of health centre directors (8/42) cited storage problems as a disadvantage and 7.7% of pharmacy managers (1/13) felt that the devices created a storage problem.

A number of survey-based studies were identified that looked at the potential benefits of advanced **misoprostol** distribution in rural settings of LMICs where the maternal mortality ratio was relatively high (20–34). The studies were conducted in Afghanistan, Bangladesh, Ethiopia (two studies), Ghana, Liberia, Madagascar, Mozambique, Nepal, Nigeria (three studies), Pakistan, South Sudan and the United Republic of Tanzania (two studies). In most instances, **misoprostol** tablets were given to trained community health workers, community health volunteers or traditional birth attendants who then supplied the tablets (usually 3 x 200 μg tablets) to pregnant women in community settings via a home visit or at an antenatal appointment during the eighth month of pregnancy. During the home visit or appointment women were also given information on PPH, the nature of the **misoprostol** tablets and how/when to take them, as well as details of potential side-effects. In most of the studies the authors concluded that the programmes were effective and feasible, although inconsistent stock supplies and the delivery of inadequate information by community health volunteers were highlighted as concerns in Nepal *(29)*.

Given the issues outlined above relating to the inconsistent supply of **oxytocin** and the additional training required to administer the drug (particularly in LMICs), it seems likely that the use of combination uterotonics (such as **oxytocin plus ergometrine** or **misoprostol plus oxytocin**) would exacerbate these issues. **Misoprostol plus oxytocin** is not a natural or synthetic drug combination, and practical considerations regarding dosing regimens (oral versus parenteral), transport and storage issues could complicate implementation in non-trial settings.

Judgement

Carbetocin	— Don't know	— Varies	— No	— Probably No	✓ Probably Yes	— Yes
Misoprostol	— Don't know	— Varies	— No	— Probably No	✓ Probably Yes	— Yes
Injectable prostaglandins	— Don't know	✓ Varies	— No	— Probably No	— Probably Yes	— Yes
Ergometrine	— Don't know	— Varies	— No	— Probably No	✓ Probably Yes	— Yes
Oxytocin plus ergometrine	— Don't know	✓ Varies	— No	— Probably No	— Probably Yes	— Yes
Misoprostol plus oxytocin	— Don't know	— Varies	— No	✓ Probably No	— Probably Yes	— Yes
Oxytocin	— Don't know	— Varies	— No	— Probably No	✓ Probably Yes	— Yes

4. Summary of judgements table

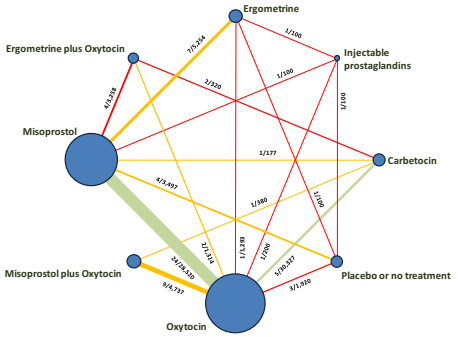
Uterotonics	Carbetocin	Misoprostol	Injectable prostaglandins	Ergometrine	Oxytocin plus ergometrine	Misoprostol plus oxytocin	Oxytocin
Desirable effects	Small	None	None	None	Small	Moderate	Reference
Undesirable effects	None	Moderate	Moderate	Moderate	Moderate	Large	Reference
Certainty of the evidence	Moderate	Moderate	Very low	Low	Moderate	Moderate	Reference
Values	Probably no important uncertainty or variability	Probably no important uncertainty or variability	Probably no important uncertainty or variability	Probably no important uncertainty or variability	Probably no important uncertainty or variability	Probably no important uncertainty or variability	Probably no important uncertainty or variability
Balance of effects	Probably favours carbetocin	Favours oxytocin	Favours oxytocin	Probably favours oxytocin	Favours oxytocin	Favours oxytocin	Reference
Resources required	Moderate costs	Varies	Large costs	Moderate costs	Negligible costs or savings	Varies	Reference
Certainty of the evidence	Low	Low	Low	Low	Low	Low	Reference
Cost-effectiveness	Probably favours oxytocin	Varies	Favours oxytocin	Favours oxytocin	Probably favours oxytocin	Varies	Reference
Equity	Varies	Probably increased	Reduced	Probably reduced	Probably reduced	Probably increased	Probably increased
Acceptability	Varies	Probably Yes	Don't know	Probably Yes	Probably Yes	Probably Yes	Varies
Feasibility	Probably Yes	Probably Yes	Varies	Probably Yes	Varies	Probably No	Probably Yes

5. Summary of Findings tables

Summary of Findings table 1

Effects of uterotonic drugs for preventing postpartum haemorrhage (by mode of birth): maternal death

Patient or population: Women in the third stage of labour
Interventions: Carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine), misoprostol plus oxytocin
Comparator (reference): Oxytocin
Outcome: Maternal death
Setting: Hospital or community setting
Source: Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis (Review). Cochrane Database Syst Rev 2018; CD011689.



Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Carbetocin	2.00 (0.37–10.92)	⨁⨁⨁◯ MODERATE	0.34 (0.00 to ∞)	Not estimable	2.00 (0.37–10.92)	⨁⨁⨁◯ MODERATE	1 per 1000	2 per 1000	1 more per 1000 (1 fewer to 10 more)
							0 per 1000 (for vaginal birth)	0 per 1000 (for vaginal birth)	0 fewer per 1000 (for vaginal birth)
							10 per 1000 (for caesarean birth)	20 per 1000 (for caesarean birth)	10 more per 1000 (6 fewer to 99 more) (for caesarean birth)
Misoprostol	0.62 (0.14–2.74)	⨁⨁⨁◯ MODERATE	1.00 (0.00 to ∞)	⨁◯◯◯ VERY LOW	0.62 (0.14–2.74)	⨁⨁⨁◯ MODERATE	1 per 1000	1 per 1000	0 fewer per 1000 (1 fewer to 2 more)
							0 per 1000 (for vaginal birth)	0 per 1000 (for vaginal birth)	0 per 1000 (for vaginal birth)
							10 per 1000 (for caesarean birth)	6 per 1000 (for caesarean birth)	4 fewer per 1000 (9 fewer to 17 more) (for caesarean birth)
Injectable prostaglandins	1.00 (0.02–49.91)	⨁◯◯◯ VERY LOW	Not estimable	—	Not estimable	—	See comments[a]	See comments[b]	See comments[c]
Ergometrine	0.91 (0.02–45.94)	⨁◯◯◯ VERY LOW	Not estimable	—	Not estimable	—	See comments[a]	See comments[b]	See comments[c]

Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Oxytocin plus ergometrine	1.00 (0.06–15.88)	⨁⨁◯◯ LOW	Not estimable	—	Not estimable	—	See comments[a]	See comments[b]	See comments[c]
Misoprostol plus oxytocin	Not estimable	—	Not estimable	—	Not estimable	—	See comments[a]	See comments[b]	See comments[c]
Oxytocin									Comparator (reference)

Note: The assumed risks in the oxytocin group are based on weighted means of baseline risks from the studies with oxytocin groups in the network meta-analysis. The corresponding risks in the carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine), and misoprostol plus oxytocin groups (and their 95% confidence interval) are based on the assumed risk in the oxytocin group and the relative effect of individual uterotonic when compared with oxytocin (and its 95% CI) derived from the network meta-analysis.

[a] There were no included studies or there were no events in the included studies to estimate the baseline risk.

[b] Absolute risk with uterotonic cannot be estimated in the absence of absolute risk with oxytocin.

[c] Risk difference cannot be estimated in the absence of absolute risks with intervention and oxytocin.

CI: confidence interval; RR: risk ratio

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group grades of evidence[1]

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.

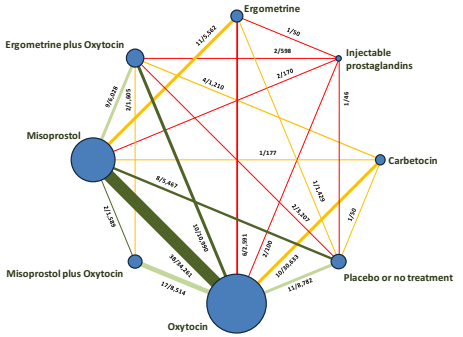
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1] Further information available at http://www.gradeworkinggroup.org

Summary of Findings table 2

Effects of uterotonic drugs for preventing postpartum haemorrhage (by mode of birth): PPH ≥ 1000 ml

Patient or population: Women in the third stage of labour
Interventions: Carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine), misoprostol plus oxytocin
Comparator (reference): Oxytocin
Outcome: PPH ≥ 1000 ml
Setting: Hospital or community setting
Source: Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis (Review). Cochrane Database Syst Rev 2018; CD011689.



Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Carbetocin	0.73 (0.45–1.19)	⨁⨁◯◯ LOW	0.30 (0.13–0.72)	⨁⨁◯◯ LOW	0.87 (0.62–1.21)	⨁◯◯◯ VERY LOW	37 per 1000	32 per 1000	5 fewer per 1000 (from 14 fewer to 8 more)
							30 per 1000 (for vaginal birth)	26 per 1000 (for vaginal birth)	4 fewer per 1000 (11 fewer to 6 more) (for vaginal birth)
							133 per 1000 (for caesarean birth)	116 per 1000 (for caesarean birth)	17 fewer per 1000 (from 51 fewer to 28 more) (for caesarean birth)
Misoprostol	1.26 (1.11–1.43)	⨁⨁⨁⨁ HIGH	1.23 (0.92–1.64)	⨁⨁⨁◯ MODERATE	1.19 (1.01–1.42)	⨁⨁⨁⨁ HIGH	37 per 1000	44 per 1000	7 more per 1000 (0 fewer to 16 more)
							30 per 1000 (for vaginal birth)	36 per 1000 (for vaginal birth)	6 more per 1000 (0 fewer to 13 more) (for vaginal birth)
							133 per 1000 (for caesarean birth)	158 per 1000 (for caesarean birth)	25 more per 1000 (1 more to 56 more) (for caesarean birth)

Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Injectable prostaglandins	1.43 (0.20–10.31)	⨁◯◯◯ VERY LOW	0.74 (0.31–1.72)	⨁◯◯◯ VERY LOW	0.88 (0.41–1.89)	⨁◯◯◯ VERY LOW	37 per 1000	33 per 1000	4 fewer per 1000 (22 fewer to 33 more)
							30 per 1000 (for vaginal birth)	27 per 1000 (for vaginal birth)	3 fewer per 1000 (18 fewer to 27 more) (for vaginal birth)
							133 per 1000 (for caesarean birth)	118 per 1000 (for caesarean birth)	15 fewer per 1000 (78 fewer to 118 more) (for caesarean birth)
Ergometrine	1.30 (0.52–3.27)	⨁◯◯◯ VERY LOW	0.61 (0.22–1.67)	⨁⨁◯◯ LOW	0.94 (0.48–1.84)	⨁⨁◯◯ LOW	37 per 1000	35 per 1000	2 fewer per 1000 (19 fewer to 31 more)
							30 per 1000 (for vaginal birth)	28 fewer per 1000 (for vaginal birth)	2 fewer per 1000 (16 fewer to 25 more) (for vaginal birth)
							133 per 1000 (for caesarean birth)	122 per 1000 (for caesarean birth)	8 fewer per 1000 (69 fewer to 112 more) (for caesarean birth)
Oxytocin plus ergometrine	0.73 (0.57–0.93)	⨁⨁⨁⨁ HIGH	1.07 (0.75–1.54)	⨁⨁⨁◯ MODERATE	0.83 (0.66–1.03)	⨁⨁⨁⨁ HIGH	37 per 1000	31 per 1000	6 fewer per 1000 (13 fewer to 1 more)
							30 per 1000 (for vaginal birth)	25 per 1000 (for vaginal birth	5 fewer per 1000 (10 fewer to 1 more) (for vaginal birth)
							133 per 1000 (for caesarean birth)	124 per 1000 (for caesarean birth)	9 fewer per 1000 (45 fewer to 4 more) (caesarean section)
Misoprostol plus oxytocin	0.87 (0.69–1.09)	⨁⨁⨁◯ MODERATE	1.17(0.47–2.86)	⨁⨁⨁⨁ HIGH	0.88 (0.70–1.11)	⨁⨁⨁⨁ HIGH	37 per 1000	30 per 1000	4 fewer per 1000 (11 fewer to 4 more)
							30 per 1000 (for vaginal birth)	26 fewer (for vaginal birth)	4 fewer per 1000 (9 fewer to 3 more) (for vaginal birth)
							133 per 1000 (for caesarean birth)	117 per 1000 (for caesarean birth)	16 fewer per 1000 (40 fewer to 13 more) (caesarean birth)

Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Oxytocin									Comparator (reference)

Note: The assumed risks in the oxytocin group are based on weighted means of baseline risks from the studies with oxytocin groups in the network meta-analysis. The corresponding risks in the Carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine) and misoprostol plus oxytocin groups (and their 95% confidence interval) are based on the assumed risk in the oxytocin group and the relative effect of individual uterotonic when compared with oxytocin (and its 95% CI) derived from the network meta-analysis.
CI: confidence interval; RR: risk ratio

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group grades of evidence

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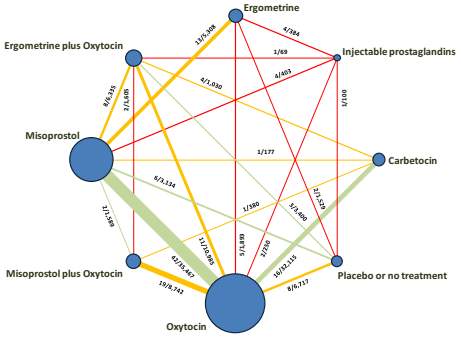
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

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.

Summary of Findings table 3

Effects of uterotonic drugs for preventing postpartum haemorrhage (by mode of birth): blood transfusion

Patient or population: Women in the third stage of labour
Interventions: carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine), misoprostol plus oxytocin
Comparator (reference): Oxytocin
Outcome: Blood transfusion
Setting: Hospital or community setting
Source: Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis (Review). Cochrane Database Syst Rev 2018; CD011689.



Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Carbetocin	0.68 (0.38–1.22)	⨁⨁⨁◯ MODERATE	0.62 (0.21–1.85)	⨁⨁◯◯ LOW	0.81 (0.49–1.32)	⨁⨁⨁◯ MODERATE	22 per 1000	18 per 1000	4 fewer per 1000 (11 fewer to 7 more)
							15 per 1000 (for vaginal birth)	12 per 1000 (for vaginal birth)	3 fewer per 1000 (5 fewer to 4 more) (for vaginal birth)
							81 per 1000 (for caesarean birth)	66 per 1000 (for caesarean birth)	15 fewer per 1000 (41 fewer to 26 more) (for caesarean birth)
Misoprostol	0.81 (0.66–1.00)	⨁⨁⨁◯ MODERATE	1.02 (0.59–1.77)	⨁⨁◯◯ LOW	0.88 (0.68–1.13)	⨁⨁⨁◯ MODERATE	22 per 1000	19 per 1000	3 fewer per 1000 (7 fewer to 3 more)
							15 per 1000 (for vaginal birth)	13 per 1000 (for vaginal birth)	2 fewer per 1000 (5 fewer to 2 more) (for vaginal birth)
							81 per 1000 (for caesarean birth)	71 per 1000 (for caesarean birth)	10 fewer per 1000 (26 fewer to 11 more) (for caesarean birth)

Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Injectable prostaglandins	1.01 (0.04–23.65)	⨁◯◯◯ VERY LOW	0.49 (0.16–1.52)	⨁◯◯◯ VERY LOW	0.66 (0.25–1.72)	⨁◯◯◯ VERY LOW	22 per 1000	15 per 1000	7 fewer per 1000 (17 fewer to 16 more)
							15 per 1000 (for vaginal birth)	10 per 1000 (for vaginal birth)	5 fewer per 1000 (11 fewer to 11 more) (for vaginal birth)
							81 per 1000 (for caesarean birth)	56 per 1000 (for caesarean birth)	28 fewer per 1000 (61 fewer to 58 more) (for caesarean birth)
Ergometrine	1.44 (0.25–6.93)	⨁◯◯◯ VERY LOW	1.01 (0.38–2.28)	⨁⨁◯◯ LOW	1.11 (0.54–2.28)	⨁⨁◯◯ LOW	22 per 1000	24 per 1000	2 more per 1000 (10 fewer to 28 more)
							15 per 1000 (for vaginal birth)	17 per 1000 (for vaginal birth)	2 more per 1000 (7 fewer to 19 more) (for vaginal birth)
							81 per 1000 (for caesarean birth)	90 per 1000 (for caesarean birth)	9 more per 1000 (37 fewer to 104 more) (for caesarean birth)
Oxytocin plus ergometrine	0.88 (0.54–1.41)	⨁⨁◯◯ LOW	0.65 (0.43–0.99)	⨁⨁◯◯ LOW	0.78 (0.59–1.03)	⨁⨁◯◯ LOW	22 per 1000	17 per 1000	5 fewer per 1000 (9 fewer to 1 more)
							15 per 1000 (for vaginal birth)	12 per 1000 (for vaginal birth)	3 fewer per 1000 (6 fewer to 0 fewer) (for vaginal birth)
							81 per 1000 (for caesarean birth)	63 per 1000 (for caesarean birth)	18 fewer per 1000 (33 fewer to 2 more) (for caesarean birth)
Misoprostol plus oxytocin	0.51 (0.38–0.67)	⨁⨁◯◯ LOW	0.77 (0.27–2.17)	⨁⨁⨁◯ MODERATE	0.52 (0.38–0.70)	⨁⨁⨁◯ MODERATE	22 per 1000	11 per 1000	11 fewer per 1000 (14 fewer to 7 fewer)
							15 per 1000 (for vaginal birth)	8 per 1000 (for vaginal birth)	7 fewer per 1000 (9 fewer to 5 fewer) (for vaginal birth)
							81 per 1000 (for caesarean birth)	42 per 1000 (for caesarean birth)	39 fewer per 1000 (50 fewer to 24 fewer) (for caesarean birth)

Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Oxytocin									Comparator (reference)

Note: The assumed risks in the oxytocin group are based on weighted means of baseline risks from the studies with oxytocin groups in the network meta-analysis. The corresponding risks in the Carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine), misoprostol plus oxytocin groups (and their 95% confidence interval) are based on the assumed risk in the oxytocin group and the relative effect of individual uterotonic when compared with oxytocin (and its 95% CI) derived from the network meta-analysis.
CI: confidence interval; RR: risk ratio

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group grades of evidence

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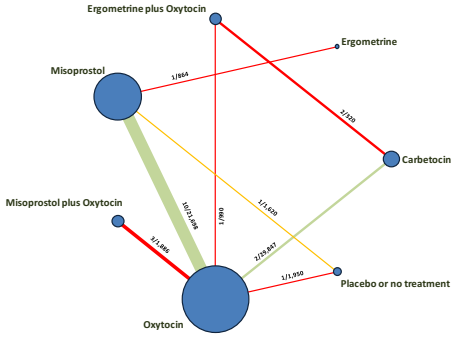
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

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.

Summary of Findings table 4

Effects of uterotonic drugs for preventing postpartum haemorrhage (by mode of birth): ICU admission

Patient or population: Women in the third stage of labour
Interventions: Carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine), misoprostol plus oxytocin
Comparator (reference): Oxytocin
Outcome: ICU admission
Setting: Hospital or community setting
Source: Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis (Review). Cochrane Database Syst Rev 2018; CD011689.



Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Carbetocin	1.16 (0.67–2.02)	⨁⨁⨁◯ MODERATE	1.56 (0.00 to ∞)	⨁◯◯◯ VERY LOW	1.16 (0.67–2.02)	⨁⨁⨁◯ MODERATE	2 per 1000	2 per 1000	0 fewer per 1000 (1 fewer to 2 more)
							2 per 1000 (for vaginal birth)	2 per 1000 (for vaginal birth)	0 fewer per 1000 (1 fewer to 2 more) (for vaginal birth)
							See comments[a] (for caesarean birth)	See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)
Misoprostol	1.16 (0.55–2.43)	⨁⨁⨁◯ MODERATE	1.05 (0.00 to ∞)	⨁◯◯◯ VERY LOW	1.16 (0.55–2.43)	⨁⨁⨁◯ MODERATE	2 per 1000	2 per 1000	0 fewer per 1000 (1 fewer to 3 more
							2 per 1000 (for vaginal birth)	2 per 1000 (for vaginal birth)	0 fewer per 1000 (1 fewer to 3 more) (for vaginal birth)
							See comments[a] (for caesarean birth)	See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)
Injectable Prostaglandins	Not reported	—	Not reported	—	Not reported	—	See comments[a]	See comments[b]	See comments[c]
Ergometrine	Not reported	—	0.39 (0.01–10.27)	⨁◯◯◯ VERY LOW	0.39 (0.01–10.27)	⨁◯◯◯ VERY LOW	2 per 1000	1 per 1000	1 fewer per 1000 (2 fewer to 19 more)
							2 per 1000 (for vaginal birth)	1 per 1000 (for vaginal birth)	1 fewer per 1000 (2 fewer to 19 more) (for vaginal birth)
							See comments[a] (for caesarean birth)	See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)

Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Oxytocin plus ergometrine	2.99 (0.12–73.32)	⨁◯◯◯ VERY LOW	1.01 (0.00 to ∞)	⨁◯◯◯ VERY LOW	2.99 (0.12–73.32)	⨁◯◯◯ VERY LOW	2 per 1000	4 per 1000	2 more per 1000 (2 fewer to 145 more)
							2 per 1000 (for vaginal birth)	4 per 1000 (for vaginal birth)	2 more per 1000 (2 fewer to 145 more) (for vaginal birth)
							See comments[a] (for caesarean birth)	See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)
Misoprostol plus oxytocin	0.50 (0.37–0.67)	⨁◯◯◯ VERY LOW	Not estimable	—	0.50 (0.05–5.47)	⨁◯◯◯ VERY LOW	2 per 1000	1 per 1000	1 fewer per 1000 (1 fewer to 1 more)
							2 per 1000 (for vaginal birth)	1 per 1000 (for vaginal birth)	1 fewer per 1000 (1 fewer to 1 more) (for vaginal birth)
							See comments[a] (for caesarean birth)	See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)
Oxytocin									Comparator (reference)

Note: The assumed risks in the oxytocin group are based on weighted means of baseline risks from the studies with oxytocin groups in the network meta-analysis. The corresponding risks in the carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine), misoprostol plus oxytocin groups (and their 95% confidence interval) are based on the assumed risk in the oxytocin group and the relative effect of individual uterotonic when compared with oxytocin (and its 95% CI) derived from the network meta-analysis.

[a] No included studies or there are no event in included studies to estimate the baseline risk.

[b] Absolute risk with uterotonic cannot be estimated in the absence of absolute risk with oxytocin.

[c] Risk difference cannot be estimated in the absence of absolute risks with intervention and oxytocin.

CI: confidence interval; RR: risk ratio

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group grades of evidence

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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.

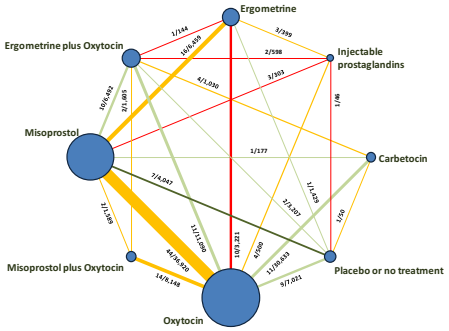
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

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.

Summary of Findings table 5

Effects of uterotonic drugs for preventing postpartum haemorrhage (by mode of birth): PPH ≥ 500 ml

Patient or population: Women in the third stage of labour
Interventions: Carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine), misoprostol plus oxytocin
Comparator (reference): Oxytocin
Outcome: PPH ≥ 500 ml
Setting: Hospital or community setting
Source: Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis (Review). Cochrane Database Syst Rev 2018; CD011689.



Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Carbetocin	0.75 (0.58–0.98)	⨁⨁⨁◯ MODERATE	0.59 (0.31–1.12)	⨁⨁◯◯ LOW	0.72 (0.56–0.93)	⨁⨁⨁◯ MODERATE	145 per 1000	104 per 1000	41 fewer per 1000 (from 64 fewer to 10 fewer)
							122 per 1000 (for vaginal birth)	87 per 1000 (for vaginal birth)	34 fewer per 1000 (from 54 fewer to 9 fewer) (for vaginal birth)
							604 per 1000 (for caesarean birth)	435 per 1000 (for caesarean birth)	169 fewer per 1000 (from 266 fewer to 42 fewer) (for caesarean birth)
Misoprostol	1.08 (0.94–1.24)	⨁⨁◯◯ LOW	1.07 (0.83–1.39)	⨁◯◯◯ VERY LOW	1.08 (0.97–1.22)	⨁⨁◯◯ LOW	145 per 1000	157 per 1000	12 more per 1000 (4 fewer to 32 more)
							122 per 1000 (for vaginal birth)	132 per 1000 (for vaginal birth)	10 more per 1000 (4 fewer to 27 more) (for vaginal birth)
							604 per 1000 (for caesarean birth)	652 per 1000 (for caesarean birth)	48 more per 1000 (18 fewer to 133 more) (for caesarean birth)

Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Injectable prostaglandins	0.84 (0.26–2.71)	⨁⨁◯◯ LOW	1.08 (0.72–1.62)	⨁◯◯◯ VERY LOW	1.05 (0.73–1.51)	⨁⨁◯◯ LOW	145 per 1000	152 per 1000	7 more per 1000 (39 fewer to 74 more)
							122 per 1000 (for vaginal birth)	128 per 1000 (for vaginal birth)	6 more per 1000 (33 fewer to 62 more) (for vaginal birth)
							604 per 1000 (for caesarean birth)	634 per 1000 (for caesarean birth)	30 more per 1000 (163 fewer to 308 more) (for caesarean birth)
Ergometrine	1.31 (0.86–1.99)	⨁◯◯◯ VERY LOW	0.96 (0.70–1.31)	⨁⨁◯◯ LOW	1.09 (0.85–1.39)	⨁⨁◯◯ LOW	145 per 1000	158 per 1000	13 more per 1000 (22 fewer to 57 more)
							122 per 1000 (for vaginal birth)	133 per 1000 (for vaginal birth)	11 more per 1000 (18 fewer to 48 more) (for vaginal birth)
							604 per 1000 (for caesarean birth)	610 per 1000 (for caesarean birth)	6 more per 1000 (91 fewer to 236 more) (for caesarean birth)
Oxytocin plus ergometrine	0.72 (0.57–0.91)	⨁⨁⨁◯ MODERATE	0.69 (0.54–0.90)	⨁⨁◯◯ LOW	0.70 (0.59–0.84)	⨁⨁⨁◯ MODERATE	145 per 1000	101 per 1000	44 fewer per 1000 (59 fewer to 23 fewer)
							122 per 1000 (for vaginal birth)	85 per 1000 (for vaginal birth)	37 fewer per 1000 (50 fewer to 20 fewer) (for vaginal birth)
							604 per 1000 (for caesarean birth)	423 per 1000 (for caesarean birth)	181 fewer per 1000 (248 fewer to 97 fewer) (for caesarean birth)

Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Misoprostol plus oxytocin	0.71 (0.59–0.85)	⨁⨁◯◯ LOW	0.79 (0.35–1.77)	⨁⨁◯◯ LOW	0.70 (0.58–0.86)	⨁⨁◯◯ LOW	145 per 1000	101 per 1000	44 fewer per 1000 (61 fewer to 20 fewer)
							122 per 1000 (for vaginal birth)	85 per 1000 (for vaginal birth)	37 fewer per 1000 (51 fewer to 17 fewer) (for vaginal birth)
							604 per 1000 (for caesarean birth)	423 per 1000 (for caesarean birth)	181 fewer per 1000 (254 fewer to 85 fewer) (for caesarean birth)
Oxytocin									Comparator (reference)

Note: The assumed risks in the oxytocin group are based on weighted means of baseline risks from the studies with oxytocin groups in the network meta-analysis. The corresponding risks in the carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine) and misoprostol plus oxytocin groups (and their 95% confidence interval) are based on the assumed risk in the oxytocin group and the relative effect of individual uterotonic when compared with oxytocin (and its 95% CI) derived from the network meta-analysis.
CI: confidence interval; RR: risk ratio

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group grades of evidence

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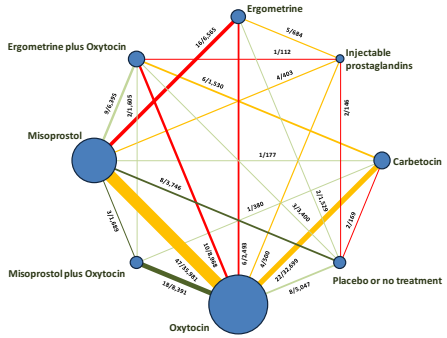
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Summary of Findings table 6

Effects of uterotonic drugs for preventing postpartum haemorrhage (by mode of birth): use of additional uterotonics

Patient or population: Women in the third stage of labour
Interventions: Carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine), misoprostol plus oxytocin
Comparator (reference): Oxytocin
Outcome: Use of additional uterotonics
Setting: Hospital or community setting
Source: Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis (Review). Cochrane Database Syst Rev 2018; CD011689.



Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Carbetocin	0.48 (0.34-0.68)	⨁⨁◯◯ LOW	0.36 (0.22-0.57)	⨁⨁◯◯ LOW	0.45 (0.34-0.59)	⨁⨁◯◯ LOW	135 per 1000	61 per 1000	74 fewer per 1000 (89 fewer to 55 fewer)
							116 per 1000 (for vaginal birth)	52 per 1000 (for vaginal birth)	64 fewer per 1000 (77 fewer to 48 fewer) (for vaginal birth)
							304 per 1000 (for caesarean birth)	137 per 1000 (for caesarean birth)	167 fewer per 1000 (201 fewer to 125 fewer) (for caesarean birth)
Misoprostol	1.01 (0.85-1.20)	⨁⨁◯◯ LOW	1.19 (0.82-1.74)	⨁⨁◯◯ LOW	1.04 (0.88-1.24)	⨁⨁◯◯ LOW	135 per 1000	140 per 1000	5 more per 1000 (16 fewer to 32 more)
							116 per 1000 (for vaginal birth)	121 per 1000 (for vaginal birth)	5 more per 1000 (14 fewer to 28 more) (for vaginal birth)
							304 per 1000 (for caesarean birth)	316 per 1000 (for caesarean birth)	12 more per 1000 (36 fewer to 73 more) (for caesarean birth)

Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Injectable prostaglandins	0.29 (0.09–0.94)	⨁⨁◯◯ LOW	0.78 (0.39–1.59)	⨁⨁◯◯ LOW	0.55 (0.31–0.96)	⨁⨁◯◯ LOW	135 per 1000	74 per 1000	61 fewer per 1000 (93 fewer to 5 fewer)
							116 per 1000 (for vaginal birth)	64 per 1000 (for vaginal birth)	52 fewer per 1000 (80 fewer to 5 fewer) (for vaginal birth)
							304 per 1000 (for caesarean birth)	167 per 1000 (for caesarean birth)	137 fewer per 1000 (210 fewer to 12 fewer) (for caesarean birth)
Ergometrine	1.46 (0.61–3.48)	⨁⨁◯◯ VERY LOW	0.84 (0.55–1.26)	⨁◯◯◯ VERY LOW	0.97 (0.69–1.36)	⨁◯◯◯ VERY LOW	135 per 1000	131 per 1000	4 fewer per 1000 (42 fewer to 49 more)
							116 per 1000 (for vaginal birth)	113 per 1000 (for vaginal birth)	3 fewer per 1000 (36 fewer to 42 more) (for vaginal birth)
							304 per 1000 (for caesarean birth)	295 per 1000 (for caesarean birth)	9 fewer per 1000 (94 fewer to 109 more) (for caesarean birth)
Oxytocin plus ergometrine	0.79 (0.59–1.07)	⨁◯◯◯ VERY LOW	0.57 (0.40–0.81)	⨁⨁◯◯ LOW	0.66 (0.51–0.85)	⨁⨁◯◯ LOW	135 per 1000	89 per 1000	46 fewer per 1000 (66 fewer to 20 fewer)
							116 per 1000 (for vaginal birth)	77 per 1000 (for vaginal birth)	39 fewer per 1000 (57 fewer to 17 fewer) (for vaginal birth)
							304 per 1000 (for caesarean birth)	201 per 1000 (for caesarean birth)	103 fewer per 1000 (149 fewer to 46 fewer) (for caesarean birth)

Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Misoprostol plus oxytocin	0.54 (0.44–0.67)	⨁⨁⨁◯ MODERATE	0.68 (0.31–1.51)	⨁⨁◯◯ LOW	0.57 (0.44–0.74)	⨁⨁⨁◯ MODERATE	135 per 1000	77 per 1000	58 fewer per 1000 (76 fewer to 35 fewer)
							116 per 1000 (for vaginal birth)	66 per 1000 (for vaginal birth)	50 fewer per 1000 (65 fewer to 30 fewer) (for vaginal birth)
							304 per 1000 (for caesarean birth)	173 per 1000 (for caesarean birth)	131 fewer per 1000 (170 fewer to 79 fewer) (for caesarean birth)
Oxytocin									Comparator (reference)

Note: The assumed risks in the oxytocin group are based on weighted means of baseline risks from the studies with oxytocin groups in the network meta-analysis. The corresponding risks in the carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine) and misoprostol plus oxytocin groups (and their 95% confidence interval) are based on the assumed risk in the oxytocin group and the relative effect of individual uterotonic when compared with oxytocin (and its 95% CI) derived from the network meta-analysis.
CI: confidence interval; RR: risk ratio

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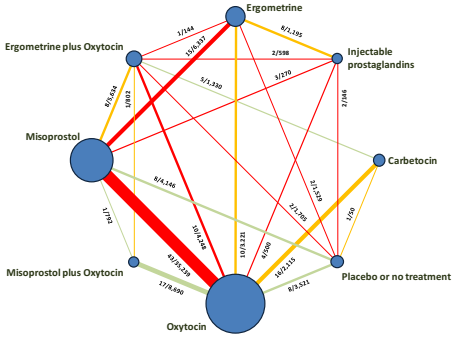
Summary of Findings table 7

Effects of uterotonic drugs for preventing postpartum haemorrhage (by mode of birth): mean blood loss (ml)

Patient or population: Women in the third stage of labour
Interventions: Carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine), misoprostol plus oxytocin
Comparator (reference): Oxytocin
Outcome: Mean blood loss (ml)
Setting: Hospital or community setting
Source: Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis (Review). Cochrane Database Syst Rev 2018; CD011689.



Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate (mean blood loss, ml)		
	MD (95% CI)	Certainty	MD (95% CI)	Certainty	MD (95% CI)	Certainty	Risk with control (oxytocin) (mean blood loss, ml)	Risk with intervention (other uterotonics)	Risk difference with intervention
Carbetocin	92.73 lower (157.83 lower to 16.69 lower)	⨁⨁◯◯ LOW	68.57 lower (147.48 lower to 10.33 higher)	⨁◯◯◯ VERY LOW	81. 39 lower (119.91 lower to 42.87 lower)	⨁⨁◯◯ LOW	301.53 (98.00–1299.00)	81.39 lower (119.91 lower to 42.87 lower)	
							271.19 (98.00–535.00) (for vaginal birth)	81.39 lower (119.91 lower to 42.87 lower) (for vaginal birth)	
							607.19 (188.00–1299.00) (for caesarean birth)	81.39 lower (119.91 lower to 42.87 lower) (for caesarean birth)	
Misoprostol	8.90 lower (23.45 lower to 5.65 higher	⨁◯◯◯ VERY LOW	6.35 lower (52.97 lower to 40.26 higher)	⨁◯◯◯ VERY LOW	9.34 lower (31.08 lower to 12.39 higher)	⨁◯◯◯ VERY LOW	301.53 (98.00–1299.00)	9.34 lower (31.08 lower to 12.39 higher)	
							271.19 (98.00–535.00) (for vaginal birth)	9.34 lower (31.08 lower to 12.39 higher) (for vaginal birth)	
							607.19 (188.00–1299.00) (for caesarean birth)	9.34 lower (31.08 lower to 12.39 higher) (for caesarean birth)	

Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate (mean blood loss, ml)		
	MD (95% CI)	Certainty	MD (95% CI)	Certainty	MD (95% CI)	Certainty	Risk with control (oxytocin) (mean blood loss, ml)	Risk with intervention (other uterotonics)	Risk difference with intervention
Injectable prostaglandins	15.83 lower (152.28 lower to 120.62 higher)	⨁◯◯◯ VERY LOW	3505 lower (91.18 lower to 21.09 higher)	⨁◯◯◯ VERY LOW	30.45 lower (77.41 lower to 16.51 higher)	⨁◯◯◯ VERY LOW	301.53 (98.00–1299.00)	30.45 lower (77.41 lower to 16.51 higher)	
							271.19 (98.00–535.00) (for vaginal birth)	30.45 lower (77.41 lower to 16.51 higher) (for vaginal birth)	
							607.19 (188.00–1299.00) (for caesarean birth)	30.45 lower (77.41 lower to 16.51 higher) (for caesarean birth)	
Ergometrine	8.09 higher (17.83 lower to 34 higher)	⨁⨁◯◯ LOW	3.07 higher (39.95 lower to 46.09 higher)	⨁⨁◯◯ LOW	4.82 higher (28.00 lower to 37.64 higher)	⨁⨁◯◯ LOW	301.53 (98.00–1299.00)	4.82 higher (28.00 lower to 37.64 higher)	
							271.19 (98.00–535.00) (for vaginal birth)	4.82 higher (28.00 lower to 37.64 higher) (for vaginal birth)	
							607.19 (188.00 –1299.00) (for caesarean birth)	4.82 higher (28.00 lower to 37.64 higher) (for caesarean birth)	
Oxytocin plus ergometrine	10.31 lower (40.32 lower to 19.70 higher)	⨁◯◯◯ VERY LOW	34.53 lower (79.23 lower to 10.17 higher)	⨁◯◯◯ VERY LOW	25.26 lower (59.15 lower to 8.64 higher)	⨁◯◯◯ VERY LOW	301.53 (98.00–1299.00)	25.26 lower (59.15 lower to 8.64 higher)	
							271.19 (98.00–535.00) (for vaginal birth)	25.26 lower (59.15 lower to 8.64 higher) (for vaginal birth)	
							607.19 (188.00 –1299.00) (for caesarean birth)	25.26 lower (59.15 lower to 8.64 higher) (for caesarean birth)	
Misoprostol plus oxytocin	87.26 lower (157.83 lower to 16.69 lower)	⨁⨁⨁◯ MODERATE	65.33 lower (288.87 lower to 158.20 higher)	⨁◯◯◯ VERY LOW	88.31 lower (127.08 lower to 49.54 lower)	⨁⨁⨁◯ MODERATE	301.53 (98.00–1299.00)	88.31 lower (127.08 lower to 49.54 lower)	
							271.19 (98.00–535.00) (for vaginal birth)	88.31 lower (127.08 lower to 49.54 lower) (for vaginal birth)	
							607.19 (188.00–1299.00) (for caesarean birth)	88.31 lower (127.08 lower to 49.54 lower) (for caesarean birth)	
Oxytocin								Comparator (reference)	

Note: The assumed risks in the oxytocin group are based on weighted means of baseline risks from the studies with oxytocin groups in the network meta-analysis. The corresponding risks in the carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine) and misoprostol plus oxytocin groups (and their 95% confidence interval) are based on the assumed risk in the oxytocin group and the relative effect of individual uterotonic when compared with oxytocin (and its 95% CI) derived from the network meta-analysis.
CI: confidence interval; MD: Mean difference

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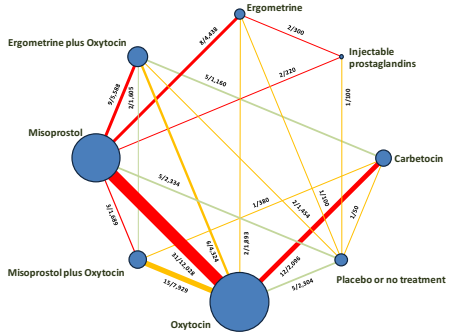
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Summary of Findings table 8

Effects of uterotonic drugs for preventing postpartum haemorrhage (by mode of birth): change in Hb (g/L)

Patient or population: Women in the third stage of labour
Interventions: Carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine), misoprostol plus oxytocin
Comparator (reference): Oxytocin
Outcome: Change in Hb (g/L)
Setting: Hospital or community setting
Source: Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis (Review). Cochrane Database Syst Rev 2018; CD011689.



Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate (g/L)		
	MD (95% CI)	Certainty	MD (95% CI)	Certainty	MD (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Carbetocin	1.66 lower (3.81 lower to 0.50 higher)	⨁◯◯◯ VERY LOW	3.27 lower (5.69 lower to 0.84 lower)	⨁◯◯◯ VERY LOW	2.18 lower (3.57 lower to 0.79 lower)	⨁⨁◯◯ LOW	11.37 (2.30–27.88)	2.18 lower (3.57 lower to 0.79 lower)	
							10.08 (2.30–25.00) (for vaginal birth)	2.18 lower (3.57 lower to 0.79 lower) (for vaginal birth)	
							14.02 (6.00–27.88) (for caesarean birth)	2.18 lower (from 3.57 lower to 0.79 lower) (for caesarean birth)	
Misoprostol	0.14 lower (0.74 lower to 0.47 higher)	⨁◯◯◯ VERY LOW	0.03 higher (2.08 lower to 2.14 higher)	⨁◯◯◯ VERY LOW	0.08 lower (0.97 lower to 0.82 higher)	⨁◯◯◯ VERY LOW	11.37 (2.30–27.88)	0.08 lower (0.97 lower to 0.82 higher)	
							10.08 (2.30–25.00) (for vaginal birth)	0.08 lower (0.97 lower to 0.82 higher) (for vaginal birth)	
							14.018 (6.00–27.88) (for caesarean birth)	0.08 lower (0.97 lower to 0.82 higher) (for caesarean birth)	

Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate (g/L)		
	MD (95% CI)	Certainty	MD (95% CI)	Certainty	MD (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Injectable prostaglandins	Not reported	—	0.60 higher (2.23 lower to 3.44 higher)	⨁◯◯◯ VERY LOW	0.60 higher (2.23 lower to 3.44 higher)	⨁◯◯◯ VERY LOW	11.37 (2.30–27.88)	0.60 higher (2.23 lower to 3.44 higher)	
							10.08 (2.30–25.00) (for vaginal birth)	0.60 higher (2.23 lower to 3.44 higher) (for vaginal birth)	
							14.02 (6.00–27.88) (for caesarean birth)	0.60 higher (2.23 lower to 3.44 higher) (for caesarean birth)	
Ergometrine	0.42 higher (0.30 lower to 1.13 higher)	⨁⨁◯◯ LOW	1.20 higher (0.78 lower to 3.17 higher)	⨁⨁◯◯ LOW	0.98 higher (0.74 lower to 2.69 higher)	⨁⨁◯◯ LOW	11.37 (2.30–27.88)	0.98 higher (0.74 lower to 2.69 higher)	
							10.08 (2.30–25.00) (for vaginal birth)	0.98 higher (0.74 lower to 2.69 higher) (for vaginal birth)	
							14.02 (6.00–27.88) (for caesarean birth)	0.98 higher (0.74 lower to 2.69 higher) (for caesarean birth)	
Oxytocin plus ergometrine	2.23 lower (from 5.24 lower to 0.77 higher)	⨁⨁◯◯ LOW	0.39 lower (from 2.07 lower to 1.29 higher)	⨁◯◯◯ VERY LOW	1.07 lower (from 2.38 lower to 0.25 higher)	⨁⨁◯◯ LOW	11.37 (2.30–27.88)	1.07 lower (2.38 lower to 0.25 higher)	
							10.08 (2.30–25.00) (for vaginal birth)	1.07 lower (2.38 lower to 0.25 higher) (for vaginal birth)	
							14.02 (6.00–27.88) (for caesarean birth)	1.07 lower (2.38 lower to 0.25 higher) (for caesarean birth)	
Misoprostol plus oxytocin	2.59 lower (3.70 lower to 1.48 lower)	⨁⨁◯◯ LOW	2.18 lower (5.85 lower to 1.50 higher)	⨁◯◯◯ VERY LOW	2.53 lower (3.80 lower to 1.26 lower)	⨁⨁◯◯ LOW	11.37 (2.30–27.88)	2.53 lower (3.80 lower to 1.26 lower)	
							10.08 (2.30–25.00) (for vaginal birth)	2.53 lower (3.80 lower to 1.26 lower) (for vaginal birth)	
							14.02 (6.00–27.88) (for caesarean birth)	2.53 lower (3.80 lower to 1.26 lower) (for caesarean birth)	
Oxytocin								Comparator (reference)	

Note: The assumed risks in the oxytocin group are based on weighted means of baseline risks from the studies with oxytocin groups in the network meta-analysis. The corresponding risks in the carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine) and Misoprostol plus oxytocin groups (and their 95% confidence interval) are based on the assumed risk in the oxytocin group and the relative effect of individual uterotonic when compared with oxytocin (and its 95% CI) derived from the network meta-analysis.
CI: confidence interval; MD: mean difference

Grading of Recommendations Assessment, Development and Evaluation (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.

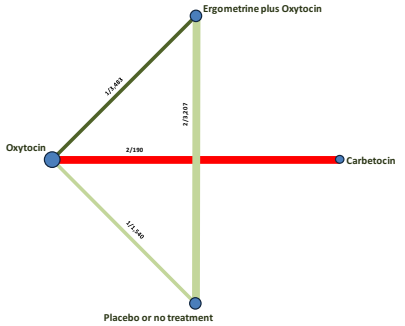
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

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.

Summary of Findings table 9

Effects of uterotonic drugs for preventing postpartum haemorrhage (by mode of birth): breastfeeding

Patient or population: Women in the third stage of labour
Interventions: Carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine), misoprostol plus oxytocin
Comparator (reference): Oxytocin
Outcome: Breastfeeding
Setting: Hospital or community setting
Source: Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis (Review). Cochrane Database Syst Rev 2018; CD011689.



Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Carbetocin	0.94 (0.86–1.03)	⨁◯◯◯ VERY LOW	0.95 (0.00 to ∞)	—	0.94 (0.86–1.03)	⨁◯◯◯ VERY LOW	849 per 1000	798 per 1000	51 fewer per 1000 (119 fewer to 25 more)
							849 per 1000 (for vaginal birth)	798 per 1000 (for vaginal birth)	51 fewer per 1000 (119 fewer to 25 more) (for vaginal birth)
							See comments[a] (for caesarean birth)	See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)
Misoprostol	Not reported	—	Not reported	—	Not reported	—	See comments[a]	See comments[b]	See comments[c]
Injectable prostaglandins	Not reported	—	Not reported	—	Not reported	—	See comments[a]	See comments[b]	See comments[c]
Ergometrine	Not reported	—	Not reported	—	Not reported	—	See comments[a]	See comments[b]	See comments[c]
Oxytocin plus ergometrine	0.99 (0.96–1.01)	⨁⨁⨁⨁ HIGH	1.03 (0.97–1.10)	⨁⨁⨁◯ MODERATE	0.99 (0.96 1.03)	⨁⨁⨁⨁ HIGH	849 per 1000	841 per 1000	8 fewer per 1000 (34 fewer to 25 more)
							849 per 1000 (for vaginal birth)	841 per 1000 (for vaginal birth)	8 fewer per 1000 (34 fewer to 25 more) (for vaginal birth)
							See comments[a] (for caesarean birth)	See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)
Misoprostol plus oxytocin	Not reported	—	Not reported	—	Not reported	—	See comments[a]	See comments[b]	See comments[c]
Oxytocin									Comparator (reference)

Note: The assumed risks in the oxytocin group are based on weighted means of baseline risks from the studies with oxytocin groups in the network meta-analysis. The corresponding risks in the carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine) and Misoprostol plus oxytocin groups (and their 95% confidence interval) are based on the assumed risk in the oxytocin group and the relative effect of individual uterotonic when compared with oxytocin (and its 95% CI) derived from the network meta-analysis.

[a] There were no included studies or there were no events in the included studies to estimate the baseline risk.

[b] Absolute risk with uterotonic cannot be estimated in the absence of absolute risk with oxytocin.

[c] Risk difference cannot be estimated in the absence of absolute risks with intervention and oxytocin.

CI: confidence interval; RR: risk ratio

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group grades of evidence

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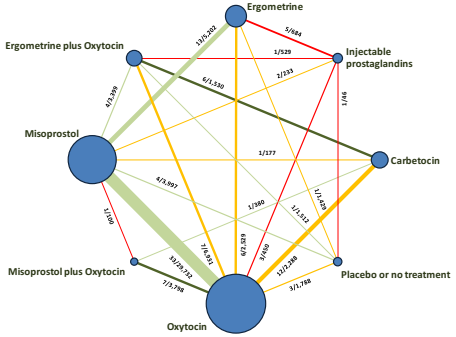
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

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.

Summary of Findings table 10

Effects of uterotonic drugs for preventing postpartum haemorrhage (by mode of birth): nausea

Patient or population: Women in the third stage of labour
Interventions: Carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine), misoprostol plus oxytocin
Comparator (reference): Oxytocin
Outcome: Nausea
Setting: Hospital or community setting
Source: Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis (Review). Cochrane Database Syst Rev 2018; CD011689.



Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Carbetocin	1.11 (0.78–1.56)	⨁⨁◯◯ LOW	0.79 (0.43–1.46)	⨁⨁◯◯ LOW	1.00 (0.71–1.41)	⨁⨁◯◯ LOW	102 per 1000	102 per 1000	0 fewer per 1000 (30 fewer to 42 more)
							86 per 1000 (for vaginal birth)	86 per 1000 (for vaginal birth)	0 fewer per 1000 (25 fewer to 35 more) (for vaginal birth)
							163 per 1000 (for caesarean birth)	163 per 1000 (for caesarean birth)	0 fewer per 1000 (47 fewer to 67 more) (for caesarean birth)
Misoprostol	1.22 (0.93–1.60)	⨁⨁⨁◯ MODERATE	2.13 (1.34–3.38)	⨁⨁◯◯ LOW	1.41 (1.10–1.81)	⨁⨁⨁◯ MODERATE	102 per 1000	144 per 1000	42 more per 1000 (10 more to 83 more)
							86 per 1000 (for vaginal birth)	121 per 1000 (for vaginal birth)	35 more per 1000 (9 more to 70 more) (for vaginal birth)
							163 per 1000 (for caesarean birth)	230 per 1000 (for caesarean birth)	67 more per 1000 (16 more to 132 more) (for caesarean birth)

Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Injectable prostaglandins	1.17 (0.42–3.41)	⨁◯◯◯ VERY LOW	2.99 (1.36–6.57)	⨁⨁◯◯ LOW	2.25 (1.16–4.39)	⨁⨁⨁◯ MODERATE	102 per 1000	230 per 1000	128 more per 1000 (16 more to 346 more)
							86 per 1000 (for vaginal birth)	193 per 1000 (for vaginal birth)	107 more per 1000 (14 more to 292 more) (for vaginal birth)
							163 per 1000 (for caesarean birth)	367 per 1000 (for caesarean birth)	204 more per 1000 (26 more to 553 more) (for caesarean birth)
Ergometrine	4.56 (1.13–18.44)	⨁⨁◯◯ LOW	2.00 (1.28–3.10)	⨁⨁⨁◯ MODERATE	2.40 (1.65–3.49)	⨁⨁⨁◯ MODERATE	102 per 1000	245 per 1000	143 more per 1000 (66 more to 254 more)
							86 per 1000 (for vaginal birth)	206 per 1000 (for vaginal birth)	120 more per 1000 (56 more to 214 more) (for vaginal birth)
							163 per 1000 (for caesarean birth)	391 per 1000 (for caesarean birth)	228 more per 1000 (106 more to 406 more) (for caesarean birth)
Oxytocin plus ergometrine	1.72 (0.84–3.53)	⨁⨁◯◯ LOW	2.35 (1.49–3.69)	⨁⨁⨁◯ MODERATE	2.03 (1.47–2.79)	⨁⨁⨁⨁ HIGH	102 per 1000	207 per 1000	105 more per 1000 (48 more to 183 more)
							86 per 1000 (for vaginal birth)	175 per 1000 (for vaginal birth)	89 more per 1000 (40 more to 154 more) (for vaginal birth)
							163 per 1000 (for caesarean birth)	331 per 1000 (for caesarean birth)	168 more per 1000 (77 more to 292 more) (for caesarean birth)

Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Misoprostol plus oxytocin	2.21 (1.19–4.10)	⨁⨁⨁⨁ HIGH	1.03 (0.36–2.97)	⨁◯◯◯ VERY LOW	1.88 (1.14–3.09)	⨁⨁⨁⨁ HIGH	102 per 1000	192 per 1000	90 more per 1000 (14 more to 213 more)
							86 per 1000 (for vaginal birth)	162 per 1000 (for vaginal birth)	76 more per 1000 (12 more to 180 more) (for vaginal birth)
							163 per 1000 (for caesarean birth)	326 per 1000 (for caesarean birth)	163 more per 1000 (23 more to 341 more) (for caesarean birth)
Oxytocin									Comparator (reference)

Note: The assumed risks in the oxytocin group are based on weighted means of baseline risks from the studies with oxytocin groups in the network meta-analysis. The corresponding risks in the carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine) and misoprostol plus oxytocin groups (and their 95% confidence interval) are based on the assumed risk in the oxytocin group and the relative effect of individual uterotonic when compared with oxytocin (and its 95% CI) derived from the network meta-analysis.
CI: confidence interval; RR: risk ratio

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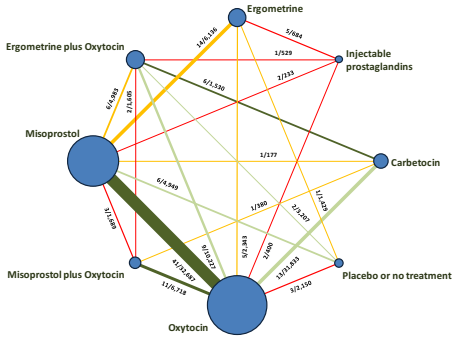
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

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.

Summary of Findings table 11

Effects of uterotonic drugs for preventing postpartum haemorrhage (by mode of birth): vomiting

Patient or population: Women in the third stage of labour
Interventions: Carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine ®), misoprostol plus oxytocin
Comparator (reference): Oxytocin
Outcome: Vomiting
Setting: Hospital or community setting
Source: Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis (Review). Cochrane Database Syst Rev 2018; CD011689.



Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Carbetocin	0.90 (0.53–1.50)	⨁⨁⨁◯ MODERATE	1.00 (0.51 1.95)	⨁⨁◯◯ LOW	0.93 (0.64–1.35)	⨁⨁⨁◯ MODERATE	28 per 1000	26 per 1000	2 fewer per 1000 (10 fewer to 10 more)
							13 per 1000 (for vaginal birth)	12 per 1000 (for vaginal birth)	1 fewer per 1000 (5 fewer to 5 more) (for vaginal birth)
							97 per 1000 (for caesarean birth)	91 per 1000 (for caesarean birth)	6 fewer per 1000 (34 fewer to 35 more) (for caesarean birth)
Misoprostol	1.51 (1.19–1.91)	⨁⨁⨁⨁ HIGH	2.73 (1.66–4.50)	⨁⨁◯◯ LOW	1.63 (1.25–2.14)	⨁⨁⨁◯ MODERATE	28 per 1000	46 per 1000	18 more per 1000 (7 more to 32 more)
							13 per 1000 (for vaginal birth)	21 per 1000 (for vaginal birth)	8 more per 1000 (3 more to 15 more) (for vaginal birth)
							97 per 1000 (for caesarean birth)	158 per 1000 (for caesarean birth)	61 more per 1000 (24 more to 111 more) (for caesarean birth)

Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Injectable prostaglandins	2.48 (0.57–10.73)	⨁◯◯◯ VERY LOW	4.07 (1.90–7.42)	⨁◯◯◯ VERY LOW	3.76 (1.90–7.42)	⨁⨁◯◯ LOW	28 per 1000	105 per 1000	77 more per 1000 (25 more to 180 more)
							13 per 1000 (for vaginal birth)	49 per 1000 (for vaginal birth)	36 more per 1000 (12 more to 83 more) (for vaginal birth)
							97 per 1000 (for caesarean birth)	365 per 1000 (for caesarean birth)	268 more per 1000 (87 more to 623 more) (for caesarean birth)
Ergometrine	3.83 (1.10–13.28)	⨁⨁◯◯ LOW	1.83 (1.19–2.84)	⨁⨁◯◯ LOW	2.36 (1.56–3.55)	⨁⨁⨁◯ MODERATE	28 per 1000	66 per 1000	38 more per 1000 (16 more to 71 more)
							13 per 1000 (for vaginal birth)	31 per 1000 (for vaginal birth)	18 more per 1000 (7 more to 33 more) (for vaginal birth)
							97 per 1000 (for caesarean birth)	229 per 1000 (for caesarean birth)	132 more per 1000 (54 more to 247 more) (for caesarean birth)
Oxytocin plus ergometrine	3.05 (1.76–5.29)	⨁⨁⨁◯ MODERATE	2.77 (1.75–4.38)	⨁⨁◯◯ LOW	2.93 (2.08–4.13)	⨁⨁⨁◯ MODERATE	28 per 1000	82 er 1000	54 more per 1000 (30 more to 88 more)
							13 per 1000 (for vaginal birth)	38 per 1000 (for vaginal birth)	25 more per 1000 (14 more to 41 more) (for vaginal birth)
							97 per 1000 (for caesarean birth)	284 per 1000 (for caesarean birth)	187 more per 1000 (105 more to 304 more) (for caesarean birth)

Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Misoprostol plus oxytocin	2.24 (1.52–3.31)	⨁⨁⨁⨁ HIGH	1.48 (0.52–4.27)	⨁◯◯◯ VERY LOW	2.11 (1.39–3.18)	⨁⨁⨁⨁ HIGH	28 per 1000	59 per 1000	31 more per 1000 (11 more to 61 more)
							13 per 1000 (for vaginal birth)	27 per 1000 (for vaginal birth)	14 more per 1000 (5 more to 28 more) (for vaginal birth)
							97 per 1000 (for caesarean birth)	205 per 1000 (for caesarean birth)	108 more per 1000 (38 more to 211 more) (for caesarean birth)
Oxytocin									Comparator (reference)

Note: The assumed risks in the oxytocin group are based on weighted means of baseline risks from the studies with oxytocin groups in the network meta-analysis. The corresponding risks in the carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine) and misoprostol plus oxytocin groups (and their 95% confidence interval) are based on the assumed risk in the oxytocin group and the relative effect of individual uterotonic when compared with oxytocin (and its 95% CI) derived from the network meta-analysis.
CI: confidence interval; RR: risk ratio

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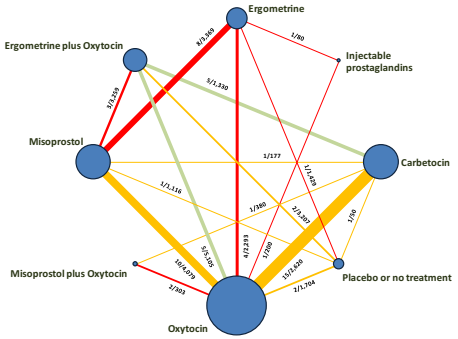
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

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.

Summary of Findings table 12

Effects of uterotonic drugs for preventing postpartum haemorrhage (by mode of birth): headache

Patient or population: Women in the third stage of labour
Interventions: Carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine), misoprostol plus oxytocin
Comparator (reference): Oxytocin
Outcome: Headache
Setting: Hospital or community setting
Source: Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis (Review). Cochrane Database Syst Rev 2018; CD011689.



Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Carbetocin	0.84 (0.63–1.12)	⨁⨁◯◯ LOW	1.46 (0.66–3.25)	⨁⨁◯◯ LOW	0.94 (0.66–1.33)	⨁⨁◯◯ LOW	171 per 1000	161 per 1000	10 fewer per 1000 (58 fewer to 56 more)
							167 per 1000 (for vaginal birth)	157 per 1000 (for vaginal birth)	10 fewer per 1000 (57 fewer to 55 more) (for vaginal birth)
							175 per 1000 (for caesarean birth)	164 per 1000 (for caesarean birth)	11 fewer per 1000 (59 fewer to 58 more) (for caesarean birth)
Misoprostol	0.88 (0.54–1.42)	⨁⨁◯◯ LOW	1.19 (0.61–2.33)	⨁⨁◯◯ LOW	0.98 (0.69–1.40)	⨁⨁◯◯ LOW	171 per 1000	168 per 1000	3 fewer per 1000 (53 fewer to 68 more)
							167 per 1000 (for vaginal birth)	164 per 1000 (for vaginal birth)	3 fewer per 1000 (52 fewer to 67 more) (for vaginal birth)
							175 per 1000 (for caesarean birth)	171 per 1000 (for caesarean birth)	4 fewer per 1000 (54 fewer to 70 more) (for caesarean birth)

Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Injectable prostaglandins	0.20 (0.01–4.11)	⨁◯◯◯ VERY LOW	4.10 (0.57–29.36)	⨁◯◯◯ VERY LOW	1.76 (0.33–9.31)	⨁◯◯◯ VERY LOW	171 per 1000	298 per 1000	130 more per 1000 (115 fewer to 1000 more)
							167 per 1000 (for vaginal birth)	291 per 1000 (for vaginal birth)	124 more per 1000 (112 fewer to 1000 more) (for vaginal birth)
							175 per 1000 (for caesarean birth)	308 per 1000 (for caesarean birth)	133 more per 1000 (117 fewer to 1000 more) (for caesarean birth)
Ergometrine	5.63 (0.93–33.96)	⨁◯◯◯ VERY LOW	1.34 (0.65–2.76)	⨁◯◯◯ VERY LOW	1.89 (1.02–3.50)	⨁⨁◯◯ LOW	171 per 1000	323 per 1000	152 more per 1000 (3 more to 428 more)
							167 per 1000 (for vaginal birth)	316 per 1000 (for vaginal birth)	149 more per 1000 (3 more to 418 more) (for vaginal birth)
							175 per 1000 (for caesarean birth)	331 per 1000 (for caesarean birth)	156 more per 1000 (2 more to 438 more) (for caesarean birth)
Oxytocin plus ergometrine	1.26 (0.79–1.99)	⨁⨁⨁◯ MODERATE	0.87 (0.48–1.58)	⨁⨁◯◯ LOW	1.08 (0.73–1.61)	⨁⨁⨁◯ MODERATE	171 per 1000	185 per 1000	14 more per 1000 (46 fewer to 104 more)
							167 per 1000 (for vaginal birth)	180 per 1000 (for vaginal birth)	13 more per 1000 (45 fewer to 102 more) (for vaginal birth)
							175 per 1000 (for caesarean birth)	191 per 1000 (for caesarean birth)	16 more per 1000 (47 fewer to 107 more) (for caesarean birth)

Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Misoprostol plus oxytocin	1.26 (0.26–6.23)	⨁⨁⨁⨁ HIGH	1.90 (0.27–13.36)	⨁⨁◯◯ LOW	1.48 (0.42–5.81)	⨁⨁◯◯ LOW	171 per 1000	253 per 1000	82 more per 1000 (99 fewer to 823 more)
							167 per 1000 (for vaginal birth)	247 per 1000 (for vaginal birth)	80 more per 1000 (97 fewer to 803 more) (for vaginal birth)
							175 per 1000 (for caesarean birth)	259 per 1000 (for caesarean birth)	84 more per 1000 (102 fewer to 842 more) (for caesarean birth)
Oxytocin									Comparator (reference)

Note: The assumed risks in the oxytocin group are based on weighted means of baseline risks from the studies with oxytocin groups in the network meta-analysis. The corresponding risks in the carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine) and misoprostol plus oxytocin groups (and their 95% confidence interval) are based on the assumed risk in the oxytocin group and the relative effect of individual uterotonic when compared with oxytocin (and its 95% CI) derived from the network meta-analysis.
CI: confidence interval; RR: risk ratio

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group grades of evidence

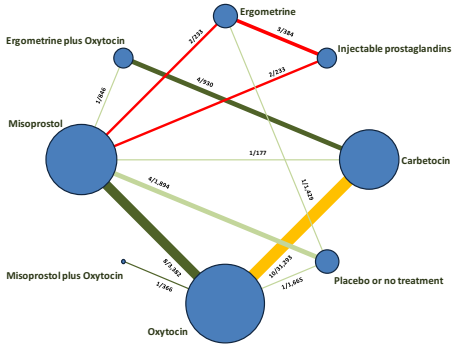
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

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.

Summary of Findings table 13



Effects of uterotonic drugs for preventing postpartum haemorrhage (by mode of birth): abdominal pain

Patient or population: Women in the third stage of labour
Interventions: Carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine), misoprostol plus oxytocin
Comparator (reference): Oxytocin
Outcome: Abdominal pain
Setting: Hospital or community setting
Source: Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis (Review). Cochrane Database Syst Rev 2018; CD011689.

Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Carbetocin	1.18 (0.97–1.44)	⨁⨁◯◯ LOW	0.89 (0.44–1.84)	⨁⨁⨁◯ MODERATE	1.13 (0.90–1.44)	⨁⨁⨁◯ MODERATE	241 per 1000	272 per 1000	31 more per 1000 (24 fewer to 106 more)
							210 per 1000 (for vaginal birth)	237 per 1000 (for vaginal birth)	27 more per 1000 (21 fewer to 92 more) (for vaginal birth)
							364 per 1000 (for caesarean birth)	411 per 1000 (for caesarean birth)	47 more per 1000 (36 fewer to 160 more) (for caesarean birth)
Misoprostol	0.91 (0.79–1.06)	⨁⨁⨁⨁ HIGH	1.17 (0.71–1.93)	⨁⨁◯◯ LOW	1.02 (0.80–1.31)	⨁⨁⨁⨁ HIGH	241 per 1000	246 per 1000	5 more per 1000 (48 fewer to 75 more)
							210 per 1000 (for vaginal birth)	214 per 1000 (for vaginal birth)	4 more per 1000 (42 fewer to 65 more) (for vaginal birth)
							364 per 1000 (for caesarean birth)	371 per 1000 (for caesarean birth)	7 more per 1000 (73 fewer to 113 more) (for caesarean birth)

Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Injectable prostaglandins	Not reported	—	1.41 (0.39–5.09)	⨁◯◯◯ VERY LOW	1.41 (0.39–5.09)	⨁◯◯◯ VERY LOW	241 per 1000	340 per 1000	99 more per 1000 (147 fewer to 986 more)
							210 per 1000 (for vaginal birth)	298 per 1000 (for vaginal birth)	88 more per 1000 (128 fewer to 859 more) (for vaginal birth)
							364 per 1000 (for caesarean birth)	517 per 1000 (for caesarean birth)	153 more per 1000 (222 fewer to 1.489 more) (for caesarean birth)
Ergometrine	Not reported	—	2.13 (0.98–4.62)	⨁◯◯◯ VERY LOW	2.13 (0.98–4.62)	⨁◯◯◯ VERY LOW	241 per 1000	513 per 1000	272 more per 1000 (5 fewer to 872 more)
							210 per 1000 (for vaginal birth)	447 per 1000 (for vaginal birth)	237 more per 1000 (4 fewer to 760 more) (for vaginal birth)
							364 per 1000 (for caesarean birth)	775 per 1000 (for caesarean birth)	411 more per 1000 (7 fewer to 1000 more)[b] (for caesarean birth)
Oxytocin plus ergometrine	Not reported	—	1.39 (0.91–2.13)	⨁⨁◯◯ LOW	1.39 (0.91–2.13)	⨁⨁◯◯ LOW	241 per 1000	335 per 1000	94 more per 1000 (22 fewer to 272 more)
							210 per 1000 (for vaginal birth)	292 per 1000 (for vaginal birth)	82 more per 1000 (19 fewer to 237 more) (for vaginal birth)
							364 per 1000 (for caesarean birth)	506 per 1000 (for caesarean birth)	142 more per 1000 (33 fewer to 411 more) (for caesarean birth)

Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Misoprostol plus oxytocin	1.93 (1.01–3.67)	⨁⨁⨁⨁ HIGH	0.90 (0.00 to ∞)[a]	Not possible to assess	1.93 (0.89–4.20)	⨁⨁⨁⨁ HIGH	241 per 1000	465 per 1000	224 more per 1000 (27 fewer to 771 more)
							210 per 1000 (for vaginal birth)	405 per 1000 (for vaginal birth)	195 more per 1000 (23 fewer to 672 more) (for vaginal birth)
							364 per 1000 (for caesarean birth)	703 per 1000 (for caesarean birth)	339 more per 1000 (40 fewer to 1000 more)[b] (for caesarean birth)
Oxytocin									Comparator (reference)

Note: The assumed risks in the oxytocin group are based on weighted means of baseline risks from the studies with oxytocin groups in the network meta-analysis. The corresponding risks in the carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine) and misoprostol plus oxytocin groups (and their 95% confidence interval) are based on the assumed risk in the oxytocin group and the relative effect of individual uterotonic when compared with oxytocin (and its 95% CI) derived from the network meta-analysis.

[a] There were no closed first-order loops for the indirect evidence, therefore it was not possible to assess the certainty of this evidence.

[b] The estimated anticipated absolute effect is based on the product of the relative risk and the baseline risk. When relative risks and/or baseline risks are high, the estimated anticipated effect can exceed 1000 per 1000. In these instances, it has been capped at 1000 per 1000.

CI: confidence interval; RR: risk ratio

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group grades of evidence

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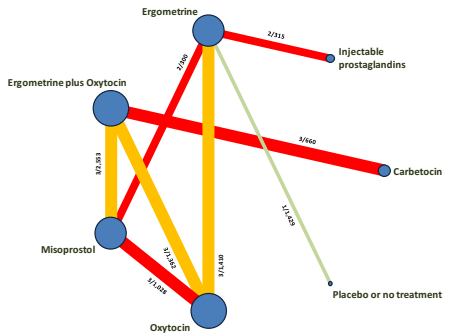
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

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.

Summary of Findings table 14

Effects of uterotonic drugs for preventing postpartum haemorrhage (by mode of birth): hypertension

Patient or population: Women in the third stage of labour
Interventions: Carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine), misoprostol plus oxytocin
Comparator (reference): Oxytocin
Outcome: Hypertension
Setting: Hospital or community setting
Source: Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis (Review). Cochrane Database Syst Rev 2018; CD011689.



Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Carbetocin	Not reported	—	1.24 (0.28–5.56)	⨁◯◯◯ VERY LOW	1.24 (0.28–5.56)	⨁◯◯◯ VERY LOW	82 per 1000	102 per 1000	20 more per 1000 (59 fewer to 374 more)
							76 per 1000 (for vaginal birth)	94 per 1000 (for vaginal birth)	18 more per 1000 (55 fewer to 347 more) (for vaginal birth)
							167 per 1000 (for caesarean birth)	207 per 1000 (for caesarean birth)	40 more per 1000 (120 fewer to 762 more) (for caesarean birth)
Misoprostol	3.64 (0.60–22.27)	⨁◯◯◯ VERY LOW	1.01 (0.28–3.65)	⨁⨁◯◯ LOW	1.50 (0.49–4.61)	⨁⨁◯◯ LOW	82 per 1000	123 per 1000	41 more per 1000 (42 fewer to 296 more)
							76 per 1000 (for vaginal birth)	114 per 1000 (for vaginal birth)	38 more per 1000 (39 fewer to 274 more) (for vaginal birth)
							167 per 1000 (for caesarean birth)	250 per 1000 (for caesarean birth)	83 more per 1000 (85 fewer to 603 more) (for caesarean birth)

Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Injectable prostaglandins	Not reported	—	1.40 (00.9–20.66)	⨁◯◯◯ VERY LOW	1.40 (0.09–20.66)	⨁◯◯◯ VERY LOW	82 per 1000	115 per 1000	33 more per 1000 (75 fewer to 1000 more)[a]
							76 per 1000 (for vaginal birth)	106 per 1000 (for vaginal birth)	30 more per 1000 (69 fewer to 1000 more)[a] (for vaginal birth)
							167 per 1000 (for caesarean birth)	234 per 1000 (for caesarean birth)	67 more per 1000 (152 fewer to 1000 more)[a] (for caesarean birth)
Ergometrine	13.39 (2.01–89.44)	⨁⨁◯◯ LOW	12.42 (0.91–168.67)	⨁◯◯◯ VERY LOW	8.54 (2.12–34.48)	⨁⨁◯◯ LOW	82 per 1000	700 per 1000	618 more per 1000 (92 more to 1000 more)[a]
							76 per 1000 (for vaginal birth)	649 per 1000 (for vaginal birth)	573 more per 1000 (85 more to 1000 more)[a] (for vaginal birth)
							167 per 1000 (for caesarean birth)	1000 per 1000 (for caesarean birth)[a,b]	1000 more per 1000 (187 more to 1000 more)[a] (for caesarean birth)[b]
Oxytocin plus ergometrine	2.00 (0.29–13.97)	⨁⨁◯◯ LOW	5.16 (0.63–42.13)	⨁◯◯◯ VERY LOW	2.48 (0.89–6.88)	⨁⨁◯◯ LOW	82 per 1000	203 per 1000	121 more per 1000 (9 fewer to 482 more)
							76 per 1000 (for vaginal birth)	188 per 1000 (for vaginal birth)	112 more per 1000 (8 fewer to 447 more) (for vaginal birth)
							167 per 1000 (for caesarean birth)	414 per 1000 (for caesarean birth)	247 more per 1000 (18 fewer to 982 more) (for caesarean birth)
Misoprostol plus oxytocin	Not reported	—	Not reported	—	Not reported	—	See comments[b]	See comments[c]	See comments[d]

Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Oxytocin									Comparator (reference)

Note: The assumed risks in the oxytocin group are based on weighted means of baseline risks from the studies with oxytocin groups in the network meta-analysis. The corresponding risks in the carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine) and misoprostol plus oxytocin groups (and their 95% confidence interval) are based on the assumed risk in the oxytocin group and the relative effect of individual uterotonic when compared with oxytocin (and its 95% CI) derived from the network meta-analysis.

[a] The estimated anticipated absolute effect is based on the product of the relative risk and the baseline risk. When relative risks and/or baseline risks are high, the estimated anticipated effect can exceed 1000 per 1000. In these instances, it has been capped at 1000 per 1000.

[b] No included studies or there are no events in included studies to estimate the baseline risk.

[c] Absolute risk with uterotonic cannot be estimated in the absence of absolute risk with oxytocin.

[d] Risk difference cannot be estimated in the absence of absolute risks with intervention and oxytocin.

CI: confidence interval; RR: risk ratio

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group grades of evidence

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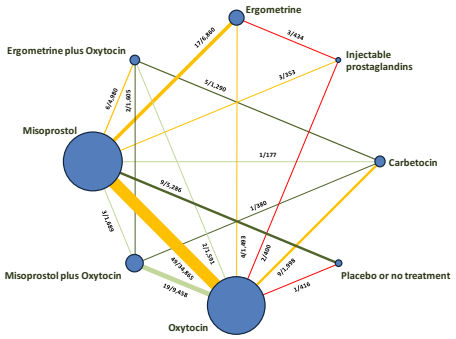
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

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.

Summary of Findings table 15

Effects of uterotonic drugs for preventing postpartum haemorrhage (by mode of birth): shivering

Patient or population: Women in the third stage of labour
Interventions: Carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine), misoprostol plus oxytocin
Comparator (reference): Oxytocin
Outcome: Shivering
Setting: Hospital or community setting
Source: Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis (Review). Cochrane Database Syst Rev 2018; CD011689.



Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Carbetocin	0.78 (0.49–1.23)	⨁⨁◯◯ LOW	0.70 (0.31–1.57)	⨁⨁◯◯ LOW	0.77 (0.46–1.29)	⨁⨁◯◯ LOW	91 per 1000	70 per 1000	21 fewer per 1000 (from 49 fewer to 26 more)
							89 per 1000 (for vaginal birth)	69 per 1000 (for vaginal birth)	20 fewer per 1000 (from 48 fewer to 26 more) (for vaginal birth)
							103 per 1000 (for caesarean birth)	79 per 1000 (for caesarean birth)	24 fewer per 1000 (from 56 fewer to 30 more) (for caesarean birth)
Misoprostol	4.02 (3.23–4.99)	⨁⨁◯◯ LOW	5.48 (2.47–12.17)	⨁⨁◯◯ LOW	4.18 (3.34–5.23)	⨁⨁◯◯ LOW	91 per 1000	380 per 1000	289 more per 1000 (213 more to 385 more)
							89 per 1000 (for vaginal birth)	372 per 1000 (for vaginal birth)	283 more per 1000 (208 more to 379 more) (for vaginal birth)
							103 per 1000 (for caesarean birth)	436 per 1000 (for caesarean birth)	333 more per 1000 (244 more to 444 more) (for caesarean birth)

Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Injectable prostaglandins	0.91 (0.11–7.73)	⨁◯◯◯ VERY LOW	0.36 (0.11–1.14)	⨁⨁◯◯ LOW	0.50 (0.19–1.31)	⨁⨁◯◯ LOW	91 per 1000	45 per 1000	46 fewer per 1000 (74 fewer to 28 more)
							89 per 1000 (for vaginal birth)	44 per 1000 (for vaginal birth)	45 fewer per 1000 (72 fewer to 28 more) (for vaginal birth)
							103 per 1000 (for caesarean birth)	51 per 1000 (for caesarean birth)	52 fewer per 1000 (83 fewer to 32 more) (for caesarean birth)
Ergometrine	1.73 (0.93–3.25)	⨁⨁◯◯ LOW	1.24 (0.79–1.99)	⨁⨁◯◯ LOW	1.31 (0.86–1.99)	⨁⨁◯◯ LOW	91 per 1000	119 per 1000	28 more per 1000 (13 fewer to 90 more)
							89 per 1000 (for vaginal birth)	117 per 1000 (for vaginal birth)	28 more per 1000 (12 fewer to 88 more) (for vaginal birth)
							103 per 1000 (for caesarean birth)	135 per 1000 (for caesarean birth)	32 more per 1000 (14 fewer to 102 more) (for caesarean birth)
Oxytocin plus ergometrine	0.96 (0.60–1.53)	⨁⨁⨁◯ MODERATE	1.57 (0.90–2.73)	⨁⨁◯◯ LOW	1.38 (0.86–2.22)	⨁⨁⨁◯ MODERATE	91 per 1000	126 per 1000	35 more per 1000 (13 fewer to 111 more)
							89 per 1000 (for vaginal birth)	123 per 1000 (for vaginal birth)	34 more per 1000 (12 fewer to 109 more) (for vaginal birth)
							103 per 1000 (for caesarean birth)	144 per 1000 (for caesarean birth)	41 more per 1000 (14 fewer to 126 more) (for caesarean birth)
Misoprostol plus oxytocin	3.38 (2.50–4.57)	⨁⨁⨁◯ MODERATE	6.34 (2.26–17.78)	⨁⨁◯◯ LOW	3.62 (2.59–5.05)	⨁⨁⨁◯ MODERATE	91 per 1000	329 per 1000	238 more per 1000 (145 more to 369 more)
							89 per 1000 (for vaginal birth)	322 per 1000 (for vaginal birth)	233 more per 1000 (142 more to 360 more) (for vaginal birth)
							103 per 1000 (for caesarean birth)	373 per 1000 (for caesarean birth)	270 more per 1000 (164 more to 417 more) (for caesarean birth)

Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Oxytocin									Comparator (reference)

Note: The assumed risks in the oxytocin group are based on weighted means of baseline risks from the studies with oxytocin groups in the network meta-analysis. The corresponding risks in the carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine) and misoprostol plus oxytocin groups (and their 95% confidence interval) are based on the assumed risk in the oxytocin group and the relative effect of individual uterotonic when compared with oxytocin (and its 95% CI) derived from the network meta-analysis.
CI: confidence interval; RR: risk ratio

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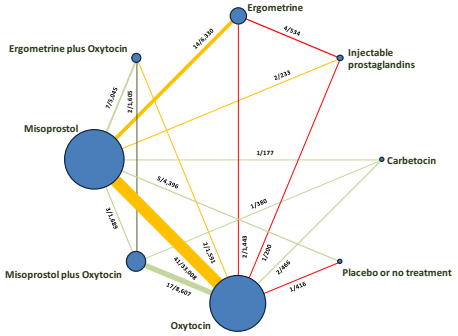
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Summary of Findings table 16

Effects of uterotonic drugs for preventing postpartum haemorrhage (by mode of birth): fever

Patient or population: Women in the third stage of labour
Interventions: Carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine), misoprostol plus oxytocin
Comparator (reference): Oxytocin
Outcome: Fever
Setting: Hospital or community setting
Source: Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis (Review). Cochrane Database Syst Rev 2018; CD011689.



Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Carbetocin	1.58 (0.27–9.35)	⨁⨁⨁◯ MODERATE	0.77 (0.18–3.42)	⨁⨁◯◯ LOW	1.07 (0.43–2.69)	⨁⨁⨁◯ MODERATE	29 per 1000	31 per 1000	2 more per 1000 (17 fewer to 49 more)
							24 per 1000 (for vaginal birth)	26 per 1000 (for vaginal birth)	2 more per 1000 (14 fewer to 41 more) (for vaginal birth)
							55 per 1000 (for caesarean birth)	59 per 1000 (for caesarean birth)	4 more per 1000 (31 fewer to 93 more) (for caesarean birth)
Misoprostol	3.75 (2.73–5.15)	⨁⨁◯◯ LOW	6.49 (2.24–18.76)	⨁⨁⨁◯ MODERATE	3.87 (2.90–5.16)	⨁⨁⨁◯ MODERATE	29 per 1000	112 per 1000	83 more per 1000 (55 more to 121 more)
							24 per 1000 (for vaginal birth)	93 per 1000 (for vaginal birth)	69 more per 1000 (46 more to 100 more) (for vaginal birth)
							55 per 1000 (for caesarean birth)	213 per 1000 (for caesarean birth)	158 more per 1000 (105 more to 229 more) (for caesarean birth)

Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Injectable prostaglandins	2.00 (0.18–21.71)	⨁◯◯◯ VERY LOW	0.96 (0.24–3.87)	⨁⨁◯◯ LOW	1.12 (0.33–3.86)	⨁⨁◯◯ LOW	29 per 1000	32 per 1000	3 more per 1000 (19 fewer to 83 more)
							24 per 1000 (for vaginal birth)	27 per 1000 (for vaginal birth)	3 more per 1000 (16 fewer to 69 more) (for vaginal birth)
							55 per 1000 (for caesarean birth)	61 per 1000 (for caesarean birth)	6 more per 1000 (37 fewer to 153 more) (for caesarean birth)
Ergometrine	2.97 (0.97–9.05)	⨁◯◯◯ VERY LOW	0.63 (0.35–1.16)	⨁⨁◯◯ LOW	0.77 (0.44–1.35)	⨁◯◯◯ VERY LOW	29 per 1000	22 per 1000	7 fewer per 1000 (16 fewer to 10 more)
							24 per 1000 (for vaginal birth)	18 per 1000 (for vaginal birth)	6 fewer per 1000 (13 fewer to 8 more) (for vaginal birth)
							55 per 1000 (for caesarean birth)	42 per 1000 (for caesarean birth)	13 fewer per 1000 (31 fewer to 18 more) (for caesarean birth)
Oxytocin plus ergometrine	1.08 (0.48–2.43)	⨁⨁◯◯ LOW	0.58 (0.25–1.39)	⨁⨁◯◯ LOW	0.70 (0.35–1.42)	⨁⨁◯◯ LOW	29 per 1000	20 per 1000	9 fewer per 1000 (19 fewer to 12 more)
							24 per 1000 (for vaginal birth)	17 per 1000 (for vaginal birth)	7 fewer per 1000 (16 fewer to 10 more) (for vaginal birth)
							55 per 1000 (for caesarean birth)	42 per 1000 (for caesarean birth)	13 fewer per 1000 (31 fewer to 19 more) (for caesarean birth)
Misoprostol plus oxytocin	2.99 (2.00–4.45)	⨁⨁⨁◯ MODERATE	5.34 (1.48–19.25)	⨁⨁◯◯ LOW	3.14 (2.20–4.49)	⨁⨁⨁◯ MODERATE	29 per 1000	91 per 1000	62 more per 1000 (35 more to 101 more)
							24 per 1000 (for vaginal birth)	75 per 1000 (for vaginal birth)	51 more per 1000 (29 more to 84 more) (for vaginal birth)
							55 per 1000 (for caesarean birth)	173 per 1000 (for caesarean birth)	118 more per 1000 (66 more to 192 more) (for caesarean birth)
Oxytocin									Comparator (reference)

Note: The assumed risks in the oxytocin group are based on weighted means of baseline risks from the studies with oxytocin groups in the network meta-analysis. The corresponding risks in the carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine) and misoprostol plus oxytocin groups (and their 95% confidence interval) are based on the assumed risk in the oxytocin group and the relative effect of individual uterotonic when compared with oxytocin (and its 95% CI) derived from the network meta-analysis.
CI: confidence interval; RR: risk ratio

Grading of Recommendations Assessment, Development and Evaluation (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.

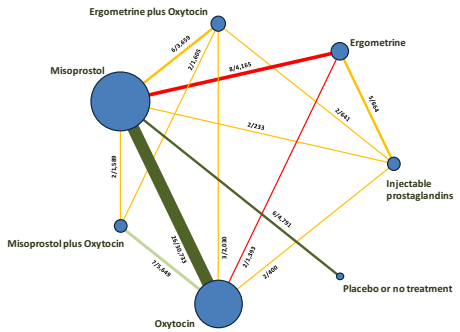
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

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.

Summary of Findings table 17

Effects of uterotonic drugs for preventing postpartum haemorrhage (by mode of birth): diarrhoea

Patient or population: Women in the third stage of labour
Interventions: Carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine), misoprostol plus oxytocin
Comparator (reference): Oxytocin
Outcome: Diarrhoea
Setting: Hospital or community setting
Source: Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis (Review). Cochrane Database Syst Rev 2018; CD011689.



Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Carbetocin	Not reported	—	Not reported	—	Not reported	—	See comments[a]	See comments[b]	See comments[c]
							See comments[a] (for vaginal birth)	See comments[b] (for vaginal birth)	See comments[c] (for vaginal birth)
							See comments[a] (for caesarean birth)	See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)
Misoprostol	2.13 (1.55–2.93)	⨁⨁⨁⨁ HIGH	3.64 (1.25–10.56)	⨁◯◯◯ VERY LOW	2.24 (1.64–3.05)	⨁⨁⨁⨁ HIGH	11 per 1000	25 per 1000	14 more per 1000 (7 more to 23 more)
							11 per 1000 (for vaginal birth)	25 per 1000 (for vaginal birth)	14 more per 1000 (7 more to 23 more) (for vaginal birth)
							See comments[a] (for caesarean birth)	See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)
Injectable prostaglandins	10.38 (1.96–54.98)	⨁⨁◯◯ LOW	28.82 (11.03–66.98)	⨁⨁◯◯ LOW	23.41 (11.03–49.70)	⨁⨁⨁◯ MODERATE	11 per 1000	254 per 1000	243 more per 1000 (110 more to 536 more)
							11 per 1000 (for vaginal birth)	254 per 1000 (for vaginal birth)	243 more per 1000 (110 more to 536 more) (for vaginal birth)
							See comments[a] (for caesarean section)	See comments[b] (for caesarean section)	See comments[c] (for caesarean section)

Uterotonic agent	Direct evidence		Indirect evidence		Network meta-analysis		Anticipated absolute effects for network meta-analysis estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with control (oxytocin)	Risk with intervention (other uterotonics)	Risk difference with intervention
Ergometrine	3.74 (0.42–33.53)	⨁◯◯◯ VERY LOW	2.30 (1.02–5.18)	⨁◯◯◯ VERY LOW	2.51 (1.20–5.26)	⨁⨁◯◯ LOW	11 per 1000	28 per 1000	17 more per 1000 (2 more to 47 more)
							11 per 1000 (for vaginal birth)	28 per 1000 (for vaginal birth)	17 more per 1000 (2 more to 47 more) (for vaginal birth)
							See comments[a] (for caesarean birth)	See comments[b] (caesarean birth)	See comments[c] (caesarean birth)
Oxytocin plus ergometrine	1.26 (0.72–2.22)	⨁⨁◯◯ LOW	2.90 (1.49–5.64)	⨁⨁◯◯ LOW	1.80 (1.18–2.75)	⨁⨁⨁◯ MODERATE	11 per 1000	20 per 1000	9 more per 1000 (2 more to 19 more)
							11 per 1000 (for vaginal birth)	20 per 1000 (for vaginal birth)	9 more per 1000 (2 more to 19 more) (for vaginal birth)
							See comments[a] (for caesarean birth)	See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)
Misoprostol plus oxytocin	2.08 (0.99–4.38)	⨁⨁⨁◯ MODERATE	3.79 (1.19–12.08)	⨁⨁◯◯ LOW	1.82 (1.12–2.98)	⨁⨁⨁⨁ HIGH	11 per 1000	23 per 1000	12 more per 1000 (0 more to 37 more)
							11 per 1000 (for vaginal birth)	23 per 1000 (for vaginal birth)	12 more per 1000 (0 fewer to 37 more) (for vaginal birth)
							See comments[a] (for caesarean birth)	See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)
Oxytocin									Comparator (reference)

Note: The assumed risks in the oxytocin group are based on weighted means of baseline risks from the studies with oxytocin groups in the network meta-analysis. The corresponding risks in the carbetocin, misoprostol, injectable prostaglandins, ergometrine, oxytocin plus ergometrine (Syntometrine) and misoprostol plus oxytocin groups (and their 95% confidence interval) are based on the assumed risk in the oxytocin group and the relative effect of individual uterotonic when compared with oxytocin (and its 95% CI) derived from the network meta-analysis.

[a] There were no included studies or there were no events in the included studies to estimate the baseline risk.

[b] Absolute risk with uterotonic cannot be estimated in the absence of absolute risk with oxytocin.

[c] Risk difference cannot be estimated in the absence of absolute risks with intervention and oxytocin.

CI: confidence interval; RR: risk ratio

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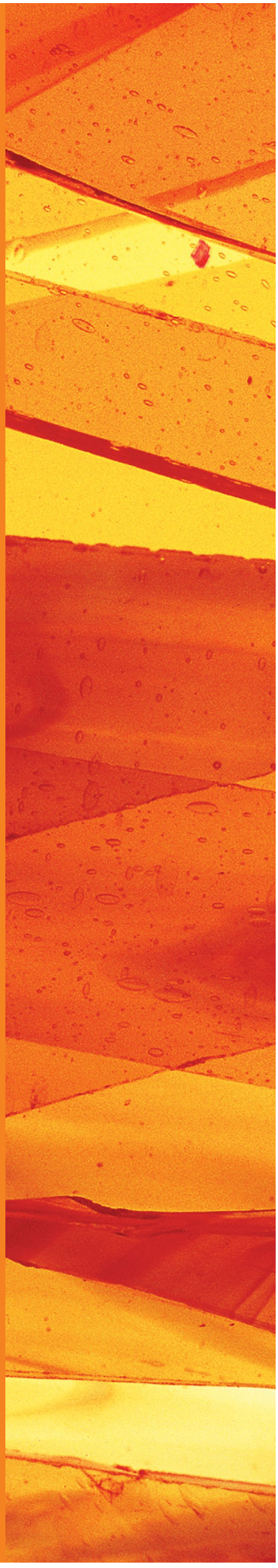

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