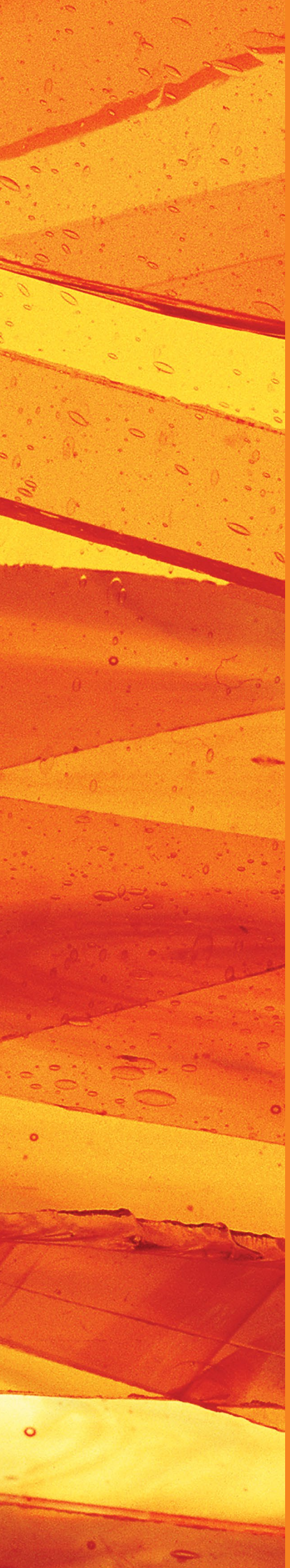

WHO recommendations

Uterotonics for the prevention of postpartum haemorrhage

Web annex 6: Injectable prostaglandins versus placebo or no treatment

EVIDENCE TO DECISION FRAMEWORK

World Health Organization

WHO recommendations

Uterotonics for the prevention of postpartum haemorrhage

Web annex 6: Injectable prostaglandins versus placebo or no treatment

Evidence to Decision Framework

World Health Organization

WHO/RHR/18.33

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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

- Prostaglandins acting on prostaglandin E_2 or prostaglandin $F_{2\alpha}$ receptors have strong uterotonic properties, and are used widely for cervical ripening, induction of labour and pregnancy termination (together with mifepristone).
- They are available in injectable, tablet or gel forms according to their intended use.
- Injectable prostaglandins include: prostaglandin $F_{2\alpha}$ analogues (carboprost), prostaglandin E_2 (dinoprostone) or prostaglandin E_2 analogues (sulprostone).

2. Question

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

> For women in the third stage of labour (P), does the use of injectable prostaglandins for prevention of postpartum haemorrhage (I), compared to placebo or no treatment (C), improve maternal and perinatal outcomes (O)?
>
> - If so, what route of administration and dosing regimen 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): Injectable prostaglandins

Comparator (C): Placebo or no treatment

Setting: Hospital and community setting

Subgroups: Women undergoing vaginal birth; women undergoing caesarean section

Priority outcomes (O):[1]

- Maternal death
- PPH ≥ 1000 ml
- Blood transfusion
- Severe maternal morbidity: intensive care unit (ICU) admissions
- Severe maternal morbidity: shock
- PPH ≥ 500 ml
- Use of additional uterotonics
- Blood loss (ml)
- Postpartum anaemia
- Breastfeeding
- Side-effects[2]

[1] 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) *(1)*. The outcomes "shock", "maternal well-being" and "maternal satisfaction" have been added as part of this update.

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

- Maternal well-being
- Maternal satisfaction

3. Assessment

3.1 Effects of interventions

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

Research evidence

Summary of evidence

Source and characteristics of studies

Evidence on the efficacy and safety of injectable prostaglandins for prevention of postpartum haemorrhage (PPH) was derived from an updated Cochrane systematic review with a network meta-analysis of all uterotonic agents for PPH prevention *(2)*. 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**.

Two randomized trials (146 women) in the network meta-analysis analysis directly compared injectable prostaglandins with placebo or no treatment. Both trials were conducted in hospital settings, one in India and the other in the Netherlands. All the women being studied had singleton pregnancies and gave birth vaginally. The studies differed in medication and dose used, one giving 500 μg sulprostone intramuscularly (IM) and the other giving 125 μg carboprost IM.

Effects of injectable prostaglandins compared with placebo or no treatment

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).

Maternal death: It is unclear whether injectable prostaglandins reduce the risk of maternal death when compared with placebo or no treatment, because certainty of the evidence was very low.

PPH ≥ 1000 ml: It is unclear whether injectable prostaglandins reduce PPH ≥ 1000 ml when compared with placebo or no treatment, because the certainty of the evidence was very low.

Blood transfusion: It is unclear whether injectable prostaglandins make a difference to the use of blood transfusion, because the certainty of the evidence was very low.

Severe maternal morbidity – ICU admission and shock: There were no data for the outcomes ICU admission or shock reported in the included trials.

PPH ≥ 500 ml: Moderate-certainty evidence suggests that injectable prostaglandins probably reduce PPH ≥ 500 ml compared with placebo or no treatment (risk ratio [RR] 0.61, 95% confidence interval [CI] 0.42–0.90).

Use of additional uterotonics: It is unclear whether injectable prostaglandins make a difference to the use of additional uterotonics when compared with placebo or no treatment, because the certainty of the evidence was very low.

Mean blood loss: Low-certainty evidence suggests that injectable prostaglandins may slightly reduce blood loss (mean difference [MD] 87.43 ml lower, 95% CI 144.93–29.93 ml lower).

Postpartum anaemia: This outcome was not directly reported in the review. The **mean change in haemoglobin level** in women before versus after birth was reported; however, the effect of the intervention is unclear because the certainty of the evidence was very low.

Breastfeeding: No trials reported on this outcome.

Any side-effect: Low-certainty evidence suggests that injectable prostaglandins may increase the risk of experiencing **nausea** (RR 1.98, 95% CI 0.89–4.43), although the range of where the actual effect may be indicates that it may make little or no difference. Low-certainty evidence suggests that injectable prostaglandins may increase the risk of **vomiting** (RR 3.69, 95% CI 1.65–8.26). Moderate-certainty evidence suggests that injectable prostaglandins probably increase the risk of **diarrhoea** (RR 29.27, 95% CI 9.57–89.48). Low-certainty evidence suggests that injectable prostaglandins may make little or no difference to the risk of **fever** (RR 1.19, 95% CI 0.30–4.77). It is unclear whether injectable prostaglandins are associated with other side-effects, including **headache**, **abdominal pain**, **hypertension** and **shivering**, because the certainty of the evidence was very low.

Maternal well-being: No trials reported on this outcome.

Maternal satisfaction: No trials reported on this outcome.

Additional considerations

Subgroup analyses did not reveal a substantial difference in the effects of prophylactic injectable prostaglandins when compared with placebo or no treatment by mode of birth (vaginal versus caesarean section) or by setting (community versus hospital).

Desirable effects

How substantial are the desirable anticipated effects of injectable prostaglandins versus placebo or no treatment?

Judgement

— Don't know	— Varies	— Trivial	✓ Small	— Moderate	— Large

Undesirable effects

How substantial are the undesirable anticipated effects of injectable prostaglandins versus placebo or no treatment?

Judgement

— Don't know	— Varies	— Large	✓ Moderate	— Small	— Trivial

Certainty of the evidence

What is the overall certainty of the evidence on effects of injectable prostaglandins versus placebo or no treatment?

— 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 injectable prostaglandins 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) (3)*. 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 by 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) (4)*. 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 also highlights 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 babies) 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

None.

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 injectable prostaglandins or placebo/no treatment?

Judgement

—	—	—	—	✓	—	—
Don't know	Varies	Favours placebo/no treatment	Probably favours placebo/no treatment	Does not favour either	Probably favours injectable prosta-glandins	Favours injectable prosta-glandins

3.3 Resources

How large are the resource requirements (costs) of injectable prostaglandins for PPH prevention?

Research evidence

A systematic review of the literature found no direct evidence on the costs and cost–effectiveness of injectable prostaglandins to prevent PPH compared with no PPH prevention *(5)*. However, as the desirable effects of injectable prostaglandins for PPH prevention are uncertain, its cost–effectiveness cannot be assessed.

Additional considerations

Injectable prostaglandins are relatively more expensive compared to other available uterotonics.

Main resource requirements

Resource	Description
Staff	Injectable prostaglandins (IM) require administration by trained maternity staff.
Training	Staff would need to receive training on the use injectable prostaglandins if they are to be introduced for PPH prevention.
Supplies	Carboprost indicative costs: ■ Cost per 250 μg: US$ 23.84 *(6)*. Other costs: ■ Needle and syringe cost: approximately US$ 0.07 *(7)*.
Equipment and infrastructure	Requires cold chain storage.
Time	IM administration takes 2 minutes (same as for oxytocin) *(8)*.
Supervision and monitoring	Supervision and monitoring to ensure appropriate use, stock availability and quality.

Resources required

Judgement

— Don't know	— Varies	✓ Large costs	— Moderate costs	— Negligible costs or savings	— Moderate savings	— Large savings

Certainty of evidence on required resources

What is the certainty of the evidence on costs?

Judgement

✓ No included studies	— Very low	— Low	— Moderate	— High

Cost–effectiveness

Judgement

✓ Don't know	— Varies	— Favours placebo/no treatment	— Probably favours placebo/no treatment	— Does not favour either	— Probably favours injectable prosta-glandins	— Favours injectable prosta-glandins

3.4 Equity

What would be the impact of injectable prostaglandins for PPH prevention on health equity?

Research evidence

There is no direct evidence on the impact of introducing injectable prostaglandins 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 coverage of health interventions and worse health outcomes than more advantaged women *(9)*. Therefore, reducing maternal morbidity due to PPH could have a positive impact on health equity and improve outcomes among disadvantaged women. However, the certainty of evidence of effects for several priority outcomes was very low. The potential costs of this uterotonic may prohibit access to women in disadvantaged regions and probably reduce equity.

Judgement

— Don't know	— Varies	✓ Reduced	— Probably reduced	— Probably no impact	— Probably increased	— Increased

3.5 Acceptability

Are injectable prostaglandins 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 (like an injectable prostaglandin) to prevent PPH if it was shown to be effective and safe *(moderate confidence) (4)*. The findings revealed that in a small number of LMIC settings, traditional birth attendants prefer to use herbal medicines with uterotonic properties to prevent PPH *(moderate confidence)*, while in several high-income countries, experienced midwives use expectant management techniques and make selective use of guideline recommendations (ignoring uterotonics), especially if the birth is perceived to be normal *(moderate confidence) (4)*.

There were no findings from studies of women's perceptions relating to the acceptability of injectable prostaglandins.

Additional considerations

None.

Judgement

✓ Don't know	— Varies	— No	— Probably No	— Probably Yes	— Yes

3.6 Feasibility

Are injectable prostaglandins for PPH prevention feasible to implement?

Research evidence

Findings from a qualitative systematic review exploring perceptions of PPH prevention and treatment by women and health care providers indicate that resource constraints may influence the use of uterotonics (like injectable prostaglandins) for PPH prevention, particularly in LMICs *(high confidence) (4)*. In a wide variety of settings, health care providers felt they did not have sufficient staff with experience of using uterotonics *(high confidence)* and needed more training in PPH management *(high confidence)*. There were no findings from the reviewed studies on women's perceptions relating to the feasibility of this particular intervention.

Additional considerations

Feasibility of using injectable prostaglandins would be affected by local availability.

Judgement

— Don't know	✓ Varies	— No	— Probably No	— Probably Yes	— Yes

4. Summary of judgements table

Desirable effects	— Don't know	— Varies		— Trivial	✓ Small	— Moderate	— Large
Undesirable effects	Don't know	— Varies		— Large	✓ Moderate	— Small	— Trivial
Certainty of the evidence	— No included studies			✓ Very low	— Low	— Moderate	— High
Values				— Important uncertainty or variability	— Possibly important uncertainty or variability	✓ Probably no important uncertainty or variability	— No important uncertainty or variability
Balance of effects	— Don't know	— Varies	— Favours placebo/no treatment	— Probably favours placebo/no treatment	✓ Does not favour either	— Probably favours injectable prosta-glandins	— Favours injectable prosta-glandins
Resources required	— Don't know	— Varies	✓ Large costs	— Moderate costs	— Negligible costs or savings	— Moderate savings	— Large savings
Certainty of the evidence on required resources	✓ No included studies			— Very low	— Low	— Moderate	— High
Cost-effectiveness	✓ Don't know	— Varies	— Favours placebo/no treatment	— Probably favours placebo/no treatment	— Does not favour either	— Probably favours injectable prosta-glandins	— Favours injectable prosta-glandins
Equity	— Don't know	— Varies	✓ Reduced	— Probably reduced	— Probably no impact	— Probably increased	— Increased
Acceptability	✓ Don't know	— Varies		— No	— Probably No	— Probably Yes	— Yes
Feasibility	— Don't know	✓ Varies		— No	— Probably No	— Probably Yes	— Yes

Judgement

We recommend against the intervention	We recommend considering the intervention only	We recommend the intervention
☑	☐ in specific contexts ☐ with targeted monitoring and evaluation ☐ in the context of rigorous research	☐

5. Summary of Findings table

Patient or population: Women in the third stage of labour
Setting: Hospital or community setting
Intervention: Injectable prostaglandins
Comparison: Placebo or no treatment
Source: Gallos ID, Papadopoulou I, Man R, Athanasopoulos N, Tobias A, Price MJ, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis. Cochrane Database of Systematic Reviews 2018:CD011689 *(2)*.

Outcomes	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 placebo or no treatment	Risk with injectable prostaglandins	Risk difference with injectable prostaglandins
Maternal death	1.00 (0.02-49.44)	⨁◯◯◯ VERY LOW	Not estimable		Not estimable		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)
PPH ≥1000 ml	0.36 (0.04-3.24)	⨁◯◯◯ VERY LOW	0.54 (0.24-1.22)	⨁◯◯◯ VERY LOW	0.52 (0.24-1.13)	⨁◯◯◯ VERY LOW	27 per 1000	14 per 1000	13 fewer per 1000 (21 fewer to 4 more)
							27 per 1000 (for vaginal birth)	(for vaginal birth)	13 fewer per 1000 (21 fewer to 4 more) (for vaginal birth)
							See comments[a] (for caesarean birth)	See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)
Blood transfusions	1.00 (0.02-49.44)	⨁◯◯◯ VERY LOW	0.39 (0.14-1.05)	⨁◯◯◯ VERY LOW	0.39 (0.14-1.08)	⨁◯◯◯ VERY LOW	27 per 1000	11 per 1000	16 fewer per 1000 (23 fewer to 2 more)
							27 per 1000 (for vaginal birth)	11 per 1000 (for vaginal birth)	16 fewer per 1000 (23 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)
Intensive care unit (ICU) admissions	Not reported	—	—	—	—	—	See commentsa	See comments[b]	See commentsc
							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 commentsc (for caesarean birth)

Outcomes	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 placebo or no treatment	Risk with injectable prostaglandins	Risk difference with injectable prostaglandins
Maternal shock	Not reported	—	—	—	—	—	See comments[a]	See comments[b]	See comments[c]
PPH ≥ 500 ml	0.55 (0.22–1.35)	⨁◯◯◯ VERY LOW	0.62 (0.41–0.93)	⨁⨁◯◯ LOW	0.61 (0.42–0.90)	⨁⨁⨁◯ MODERATE	255 per 1000	156 per 1000	99 fewer per 1000 (148 fewer to 25 fewer)
							255 per 1000 (for vaginal birth)	156 per 1000 (for vaginal birth)	99 fewer per 1000 (148 fewer to 25 fewer) (for vaginal birth)
							320 per 1000 (for caesarean birth)	195 per 1000 (for caesarean birth)	125 fewer per 1000 (186 fewer to 32 fewer) (for caesarean birth)
Use of additional uterotonics	0.66 (0.21–2.09)	⨁◯◯◯ VERY LOW	0.19 (0.10–0.37)	⨁⨁◯◯ LOW	0.23 (0.13–0.42)	⨁◯◯◯ VERY LOW	211 per 1000	49 per 1000	162 fewer per 1000 (184 fewer to 122 fewer)
							193 per 1000 (for vaginal birth)	44 per 1000 (for vaginal birth)	149 fewer per 1000 (168 fewer to 112 fewer) (for vaginal birth)
							746 per 1000 (for caesarean birth)	172 per 1000 (for vaginal birth)	574 fewer per 1000 (649 fewer to 433 fewer) (for caesarean birth)
Mean blood loss (ml)	MD 95.17 ml lower (296.09 ml lower to 105.75 ml higher)	⨁◯◯◯ VERY LOW	MD 91.44 ml lower (155.66 ml lower to 27.22 ml lower)	⨁◯◯◯ VERY LOW	MD 87.43 ml lower (144.93 ml lower to 29.93 ml lower)	⨁⨁◯◯ LOW	The mean blood loss was 295 ml (range across placebo groups: 167.4 to 853 ml)	The mean blood loss with injectable prostaglandins was on average 87.43 ml lower (range: 144.93 ml lower to 29.93 ml lower)	
							The mean blood loss for vaginal birth was 294 ml (range: 167.4 to 680 ml)	The mean blood loss with injectable prostaglandins was on average 87.43 ml lower (range: 144.93 ml lower to 29.93 mL lower) (for vaginal birth)	
							See comments[a] (for caesarean birth)	See comments[c] (for caesarean birth)	

Outcomes	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 placebo or no treatment	Risk with injectable prostaglandins	Risk difference with injectable prostaglandins
Change in haemoglobin (Hb) (g/L)	MD 0.90 g/L higher (0.56 g/L higher to 1.24 g/L higher)	⨁⨁◯◯ LOW	MD 3.10 g/L lower (7.00 g/L lower to 0.80 g/L higher)	⨁◯◯◯ VERY LOW	MD 1.54 g/L lower (4.59 g/L lower to 1.52 g/L higher)	⨁◯◯◯ VERY LOW	The mean change in Hb was 8.1 g/L (range: 6.0 to 13.5 g/L)	The mean blood loss with injectable prostaglandins was on average 1.54 g/L lower (range: 4.59 g/L lower to 1.52 g/L higher)	
							The mean change in Hb for vaginal birth was 8.1 g/L (range: 6.0 to 13.5 g/L)	The mean blood loss with injectable prostaglandins was on average 1.54 g/L lower (range: 4.59 g/L lower to 1.52 g/L higher) (for vaginal birth)	
							See comments[a] (for caesarean birth)	See comments[c] (for caesarean birth)	
Breastfeeding	Not reported	—	—	—	—	—	746 per 1000	See comments[b]	See comments[c]
							746 per 1000 (for vaginal birth)	See comments[b] (for vaginal birth)	See comments[c] (for vaginal birth)
							See comments[a] (for caesarean birth)	See commentsb (for caesarean birth)	See comments[c] (for caesarean birth)
Nausea	0.36 (0.02–8.46)	⨁◯◯◯ VERY LOW	2.23 (0.97–5.09)	⨁⨁◯◯ LOW	1.98 (0.89–4.43)	⨁⨁◯◯ LOW	37 per 1000	1 more per 1000	36 more per 1000 (4 fewer to 127 more)
							37 per 1000 (for vaginal birth)	1 more per 1000 (for vaginal birth)	36 more per 1000 (4 fewer to 127 more) (for vaginal birth)
							See comments[a] (for caesarean birth)	See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)
Vomiting	Not reported	—	3.62 (1.63–8.04)[d]	⨁◯◯◯ VERY LOW	3.69 (1.65–8.26)	⨁⨁◯◯ LOW	34 per 1000	125 more per 1000	91 more per 1000 (22 more to 247 more)
							34 per 1000 (for vaginal birth)	125 more per 1000 (for vaginal birth)	91 more per 1000 (22 more to 247 more) (for vaginal birth)
							See comments[a] (for caesarean birth)	See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)

Outcomes	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 placebo or no treatment	Risk with injectable prostaglandins	Risk difference with injectable prostaglandins
Headache	Not reported	—	2.51 (0.43–14.56)[d]	⨁◯◯◯ VERY LOW	2.55 (0.43–14.99)	⨁◯◯◯ VERY LOW	12 per 1000	31 more per 1000	19 more per 1000 (7 fewer to 168 more)
							12 per 1000 (for vaginal birth)	31 more per 1000 (for vaginal birth)	19 more per 1000 (7 fewer to 168 more) (for vaginal birth)
							See comments[a] (for caesarean birth)	See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)
Abdominal pain	Not reported	—	1.41 (0.39–5.06)[d]	⨁◯◯◯ VERY LOW	1.42 (0.40–5.10)	⨁◯◯◯ VERY LOW	339 per 1000	481 more 1000	142 more per 1000 (203 fewer to 1390 more)
							339 per 1000 (for vaginal birth)	481 more 1000 (for vaginal birth)	142 more per 1000 (203 fewer to 1390 more) (for vaginal birth)
							See comments[a] (for caesarean birth)	See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)
Hypertension	Not reported	—	1.17 (0.08–18.30)[d]	⨁◯◯◯ VERY LOW	1.17 (0.08–18.30)	⨁◯◯◯ VERY LOW	7 per 1000	8 more per 1000	1 more per 1000 (6 fewer to 119 more)
							7 per 1000 (for vaginal birth)	8 more per 1000 (for vaginal birth)	1 more per 1000 (6 fewer to 119 more) (for vaginal birth)
							See comments[a] (for caesarean birth)	See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)
Shivering	Not reported	—	0.34 (0.12–1.03)[d]	⨁⨁◯◯ LOW	0.35 (0.12–1.02)	⨁⨁◯◯ LOW	148 per 1000	52 less per 1000	96 fewer per 1000 (130 fewer to 3 more)
							148 per 1000 (for vaginal birth)	52 less per 1000 (for vaginal birth)	96 fewer per 1000 (130 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)

Outcomes	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 placebo or no treatment	Risk with injectable prostaglandins	Risk difference with injectable prostaglandins
Fever	Not reported	—	1.19 (0.30–4.74)[d]	⨁⨁◯◯ LOW	1.19 (0.30–4.77)	⨁⨁◯◯ LOW	29 per 1000 (for vaginal birth)	35 more per 1000 (for vaginal birth)	6 more per 1000 (20 fewer to 108 more) (for vaginal birth)
							29 per 1000 (for vaginal birth)	35 more per 1000 (for vaginal birth)	6 more per 1000 (20 fewer to 108 more) (for vaginal birth)
							See comments[a] (for caesarean birth)	See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)
Diarrhoea	Not reported	—	25.48 (8.60–75.43)[d]	⨁⨁◯◯ LOW	29.27 (9.57–89.48)	⨁⨁⨁◯ MODERATE	6 per 1000	176 more per 1000	170 more per 1000 (51 more to 531 more)
							6 per 1000 (for vaginal birth)	176 more per 1000 (for vaginal birth)	170 more per 1000 (51 more to 531 more) (for vaginal birth)
							See comments[a] (for caesarean birth)	See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)

Note: The assumed risks in the placebo or no treatment group are based on weighted means of baseline risks from the studies with placebo or no treatment groups in the network meta-analysis. The corresponding risks in the oxytocin group (and their 95% confidence interval) are based on the assumed risk in the placebo or no treatment group and the relative effect of 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 injectable prostaglandins cannot be estimated in the absence of absolute risk with placebo or no treatment.

[c] Risk difference cannot be estimated in the absence of absolute risks with placebo or no treatment and injectable prostaglandins.

[d] The included studies did not provide any direct evidence for this outcome, therefore the effect estimate from the indirect evidence is identical to the network effect estimate.

CI: confidence interval; Hb: haemoglobin; MD: mean difference 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/

6. References

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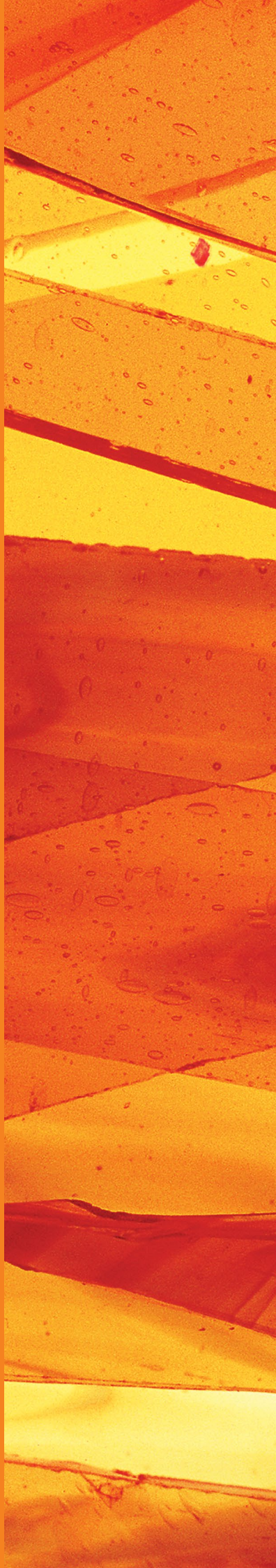

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