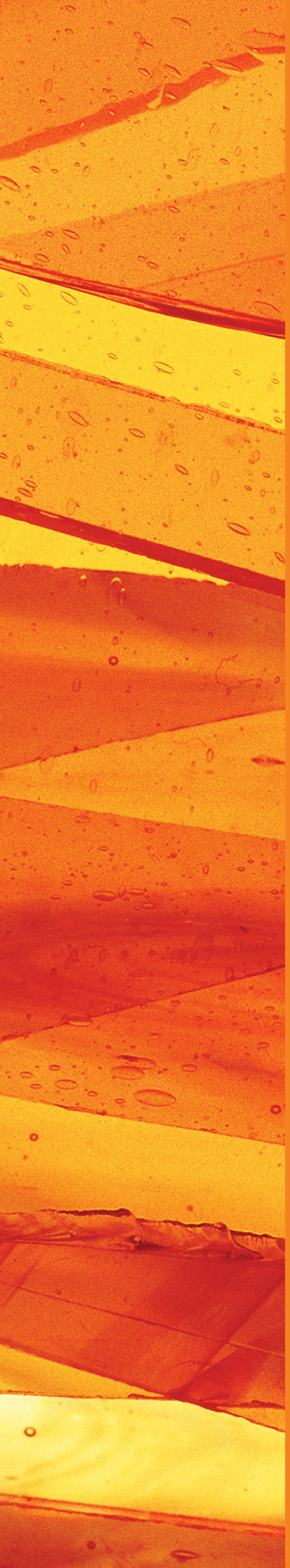

WHO recommendations
Uterotonics for the prevention of postpartum haemorrhage

Web annex 5:
Oxytocin and ergometrine versus placebo or no treatment

EVIDENCE TO DECISION FRAMEWORK

World Health Organization

WHO recommendations

Uterotonics for the prevention of postpartum haemorrhage

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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

- The intervention medication is a combination of oxytocin plus ergometrine (such as Syntometrine).
- Trials have used variable doses of oxytocin (5, 10 or 20 international units [IU]) and ergometrine (200 μg or 500 μg); however, the formulation of Syntometrine (500 μg ergometrine maleate plus 5 IU oxytocin) for intramuscular (IM) injection was most commonly used.
- Ergometrine is an ergot alkaloid that increases uterine muscle tone by causing sustained uterine contractions. After IM injection, it has a latent phase of 2–5 minutes. The plasma half-life is 30–120 minutes. It is unstable in heat, and is vasoconstrictive.
- Oxytocin produces rhythmic uterine contractions and has a short half-life of about 3–5 minutes. It is deactivated in the gastrointestinal tract and thus its main route of administration is parenteral. When given intramuscularly, it takes 3–7 minutes to take effect, but effects will last up to 1 hour. It is unstable in ambient temperatures and requires storage and transport via cold chain to ensure effectiveness.

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 oxytocin plus ergometrine for prevention of postpartum haemorrhage (I) compared with 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): All women in the third stage of labour

Intervention (I): Oxytocin plus ergometrine

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

[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.

- Use of additional uterotonics
- Blood loss (ml)
- Postpartum anaemia
- Breastfeeding
- Side-effects[1]
- Maternal well-being
- Maternal satisfaction

3. Assessment

3.1 Effects of interventions

What is the effect of oxytocin plus ergometrine for PPH prevention on the priority outcomes?

Research evidence

Summary of evidence

Source and characteristics of studies

Evidence on the efficacy and safety of oxytocin plus ergometrine 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

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

- 26 trial arms (6.3%) used misoprostol plus oxytocin
- 17 trial arms (4.1%) used injectable prostaglandins.

Three randomized trials (3400 women) in the network meta-analysis directly compared prophylactic oxytocin plus ergometrine versus placebo or no treatment. All trials were conducted in hospital settings. Two trials were carried out in the United Kingdom of Great Britain and Northern Ireland, and the other was conducted in the United States of America (USA). The parity of participants varied between studies; however, only women with singleton pregnancies who gave birth vaginally were included. The intervention was given intramuscularly in all studies, and the comparison was always "no treatment" (no studies compared with placebo).

- Two studies (1888 women) compared 500 μg of ergometrine plus 5 IU oxytocin IM versus no treatment.
- One study (1512 women) compared an unspecified dose of oxytocin plus ergometrine IM versus no treatment.

Prophylactic oxytocin plus ergometrine versus 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 oxytocin plus ergometrine reduces the risk of maternal death when compared with placebo or no treatment, because the certainty of the evidence is very low.

PPH ≥1000 ml: Moderate-certainty evidence suggests that oxytocin plus ergometrine probably reduces PPH 1000 ml compared with no treatment (risk ratio [RR] 0.49, 95% confidence interval [CI] 0.38–0.63).

Blood transfusion: When compared with no treatment, moderate-certainty evidence suggests that oxytocin plus ergometrine probably reduces the use of blood transfusion (RR 0.46, 95% CI 0.31–0.69).

Severe maternal morbidity – ICU admissions: It is unclear whether oxytocin plus ergometrine reduces ICU admissions when compared with no treatment, because the certainty of the evidence is very low. There were no data for the outcome "shock" reported in the included trials.

PPH ≥500 ml: Moderate-certainty evidence suggests that oxytocin plus ergometrine probably reduces PPH ≥ 500 ml compared with no treatment (RR 0.41, 95% CI 0.33–0.51).

Use of additional uterotonics: When compared with no treatment, low-certainty evidence suggests that oxytocin plus ergometrine may reduce the use of additional uterotonics (RR 0.28, 95% CI 0.20–0.39).

Mean blood loss: Low-certainty evidence suggests that blood loss may on average be slightly less among women receiving oxytocin plus ergometrine compared with women receiving no treatment (mean difference [MD] 82.24 ml lower, 95% CI 130.59–33.89 ml lower).

Postpartum anaemia: This outcome was not directly reported in the review. However, there is low-certainty evidence to suggest that the **mean change in haemoglobin level** before versus after birth may be slightly less among women receiving oxytocin plus ergometrine compared with those receiving no treatment (MD 3.21 g/L lower, 95% CI 5.13–1.29 g/L lower).

Breastfeeding: Moderate-certainty evidence suggests that oxytocin plus ergometrine probably makes little or no difference to the proportion of women who are breastfeeding at the time of discharge from hospital (RR 1.01, 95% CI 0.97–1.05).

Any side-effect: Moderate-certainty evidence suggests that oxytocin plus ergometrine probably increases women's risk of experiencing **nausea** (RR 1.78, 95% CI 1.04–3.08) and **vomiting** (RR 2.88, 95% CI 1.73–4.78) when compared with no treatment. Low-certainty evidence suggests that, when compared with no treatment, oxytocin plus ergometrine has little or no effect on the risk of **headache** (RR 1.57, 95% CI 0.80–3.03), **hypertension** (RR 2.08, 95% CI 0.25–17.16) and **diarrhoea** (RR 2.25, 95% CI 0.89–5.71), but the confidence intervals are wide. Moderate-certainty evidence suggests that oxytocin plus ergometrine may have little or no effect on the risk of **abdominal pain** (RR 1.40, 95% CI 0.83–2.36) or **fever** (RR 0.74, 95% CI 0.28–1.95), but the confidence intervals are wide. Low-certainty evidence suggests that oxytocin plus ergometrine may make little or no difference to the risk of **shivering** (RR 0.96, 95% CI 0.49–1.89).

Maternal well-being: This outcome was reported in eight variables by one trial (1447 women):

- General health at six weeks postpartum (worse than pre-pregnancy): Low-certainty evidence suggests that oxytocin plus ergometrine may make little or no difference to women's general health at six weeks postpartum compared with no treatment (RR 0.99, 95% CI 0.71–1.37).
- General health at six weeks postpartum (exhausted since birth): Moderate-certainty evidence suggests that oxytocin plus ergometrine probably makes little or no difference to women feeling exhausted since birth at six weeks postpartum compared with no treatment (RR 0.95, 95% CI 0.79–1.15).
- General health at six weeks postpartum (exhausted at six weeks): Low-certainty evidence suggests that oxytocin plus ergometrine may make little or no difference to women feeling exhausted at six weeks postpartum compared with no treatment (RR 0.95, 95% CI 0.74–1.21).
- General health at six weeks postpartum (blues): Moderate-certainty evidence suggests that oxytocin plus ergometrine probably makes little or no difference to women experiencing postpartum blues at six weeks postpartum compared with no treatment (RR 0.93, 95% CI 0.83–1.04).
- General health at six weeks postpartum (depressed): Low-certainty evidence suggests that oxytocin plus ergometrine may make little or no difference to women experiencing depression at six weeks postpartum compared with no treatment (RR 1.22, 95% CI 0.84–1.78).
- General health at six weeks postpartum (help for depression): Low-certainty evidence suggests that oxytocin plus ergometrine may make little or no difference to women looking for help for depression at six weeks postpartum compared with no treatment (RR 1.05, 95% CI 0.8–1.35).
- General health at six weeks postpartum (admission to hospital for depression): It is uncertain whether oxytocin plus ergometrine reduces admissions to hospital for depression at six weeks postpartum compared with no treatment because the certainty of this evidence is very low (1 study, 1447 women; RR 3.06, 95% CI 0.12–75.06).
- General health at six weeks postpartum (no health problems reported): Moderate-certainty evidence suggests that oxytocin plus ergometrine probably makes little or no difference to women reporting health problems at six weeks postpartum compared with no treatment (RR 0.95, 95% CI 0.90–1.01).

Maternal satisfaction: This outcome was reported in two variables by one trial (1507 women):

- Satisfied with third-stage management: Moderate-certainty evidence suggests that oxytocin plus ergometrine probably makes little or no difference to satisfaction with third-stage management compared with no treatment (RR 1.03, 95% CI 1–1.05).
- Felt in control during the third stage: Moderate-certainty evidence suggests that oxytocin plus ergometrine probably decreased women's feeling of being in control during the third stage compared with no treatment (RR 0.95, 95% CI 0.91–0.99).

Additional considerations

Subgroup analyses did not reveal a substantial difference in the effects of oxytocin plus ergometrine on the above outcomes when compared with placebo or no treatment by mode of birth (vaginal versus caesarean section) or by setting (community versus hospital).

We did not identify any previous systematic reviews that have compared the effects of prophylactic oxytocin plus ergometrine versus placebo or no treatment.

Caution should be exercised when using ergot derivatives (such as ergometrine) for the prevention of PPH, as these drugs have clear contraindications in women with hypertensive disorders. Thus, it is probably safer to avoid the use of ergot derivatives in unscreened populations *(1)*.

Desirable effects

How substantial are the desirable anticipated effects of oxytocin plus ergometrine versus placebo or no treatment?

Judgement

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

Undesirable effects

How substantial are the undesirable anticipated effects of oxytocin plus ergometrine 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 oxytocin plus ergometrine 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 oxytocin plus ergometrine 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 a 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 oxytocin plus ergometrine or placebo/no treatment?

Judgement

— Don't know	— Varies	— Favours placebo/no treatment	— Probably favours placebo/no treatment	— Does not favour either	✓ Probably favours oxytocin plus ergometrine	— Favours oxytocin plus ergometrine

3.3 Resources

How large are the resource requirements (costs) of oxytocin plus ergometrine for PPH prevention?

Research evidence

A systematic review of the literature found no direct evidence on the costs and cost-effectiveness of oxytocin plus ergometrine to prevent PPH compared with no PPH prevention *(5)*. However, indirect evidence on cost-effectiveness of PPH prevention from studies of other uterotonics *(6–11)* suggests that oxytocin plus ergometrine compared with no PPH prevention might be cost-effective because the desirable effects are probably substantial.

The review also found a United Kingdom cost-effectiveness analysis that compared different uterotonics with each other *(12)*. This good-quality study concluded that oxytocin plus ergometrine might be the most cost-effective uterotonic agent for vaginal and caesarean birth, when adverse events were not considered, but its cost ranking dropped when adverse events were considered. Costings and relative effects related to adverse events of the different uterotonics were fairly uncertain in this study, however, which undermined the certainty of the study findings.

Additional considerations

- Oxytocin plus ergometrine requires refrigerated storage and transport *(8)*.
- Ergometrine is contraindicated in severe hypertension and eclampsia. Thus, its use might be associated with higher staff costs (i.e. for training, supervision and/or monitoring) and might be less feasible in settings with few skilled birth attendants and poor referral systems.

Main resource requirements

Resource	Description
Staff	Oxytocin plus ergometrine requires administration by trained maternity staff.
Training	Training to administer injections, and to monitor and manage side-effects and complications, is part of maternity staff training. However, additional training would be required if oxytocin plus ergometrine is to be introduced in settings where it has not previously been available (including importance of blood pressure measurement).
Supplies	Ergometrine indicative cost: ■ Cost per 500 μg: US$ 1.97 *(13)*. Other costs: ■ Needle and syringe cost: approximately US$ 0.07 *(8)*.
Equipment and infrastructure	Cold chain storage and transport costs: ■ Cost per birth: possibly US$ 0.84 in a low-resource setting *(14)*. Other costs: ■ Sphygmomanometer for measuring blood pressure prior to administration.
Time	It takes 1–2 minutes to measure blood pressure prior to administration. IM administration takes 2 minutes (same as for oxytocin alone) *(15)*.
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 oxytocin plus ergometrine	— Favours oxytocin plus ergometrine

3.4 Equity

What would be the impact of oxytocin plus ergometrine for PPH prevention on health equity?

Research evidence

According to the findings from a qualitative systematic review looking at the prevention and treatment of PPH, inconsistent stock levels and the heat sensitivity of medications such as oxytocin (a component of the fixed-dose combination oxytocin plus ergometrine) may limit use in low-resource settings in LMICs, particularly in isolated rural areas where the need is arguably greatest *(moderate confidence) (4)*. In some contexts (e.g. India and Sierra Leone), supply issues have resulted in women and health care professionals turning to private suppliers to purchase oxytocin, at additional cost to themselves, in order to fulfil guideline recommendations.

Additional considerations

- The 2015 World Health Organization (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 *(16)*. Therefore, reducing maternal morbidity due to PPH could have a positive impact on health equity and improve outcomes among disadvantaged women. Reducing the need for additional interventions to treat PPH (such as additional uterotonics and blood transfusion) would probably reduce inequities, especially in contexts where health services are covered through out-of-pocket means.
- Using ergometrine routinely in low-resource settings where there are high rates of pre-eclampsia/eclampsia, limited screening for hypertensive disorders of pregnancy and limited capability to manage side-effects and complications, may potentially reduce health equity.

Judgement

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

3.5 Acceptability

Is oxytocin plus ergometrine 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 indicate that providers recognize the benefits of using oxytocin to prevent PPH and hasten the delivery of the placenta *(moderate confidence)* but do not discuss oxytocin use in conjunction with ergometrine *(4)*.

In some LMIC settings, providers have reservations about the storage of heat-sensitive uterotonics in areas with limited/inconsistent electricity supplies. Some providers also

hold the perception that oxytocin may cause retained placenta when administered preventatively or even contribute to PPH when given to induce labour *(moderate confidence)*. 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 and make selective use of guideline recommendations (ignoring oxytocin use), 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 this intervention.

Additional considerations

In a survey-based evaluation of prefilled oxytocin Uniject devices (containing 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 *(17)*. 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".

Judgement

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

3.6 Feasibility

Is oxytocin plus ergometrine 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 suggest that resource constraints may influence effective use of this uterotonic combination for PPH prevention, particularly in LMICs *(high confidence) (4)*. Inconsistent supplies and concerns about storage hinder utilization, and a lack of experienced staff to administer the injection limits use in certain contexts *(high confidence)*. The findings indicated that in a wide variety of settings, health care providers feel they need more training in PPH management on when/how to administer oxytocin *(high confidence)*. In 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, though TBAs felt they were competent enough and rarely had to deal with a PPH *(moderate confidence) (4)*.

There were no findings from the studies on women's perceptions relating to the feasibility of this intervention.

Additional considerations

Given the issues outlined above relating to the inconsistent supply of oxytocin and the additional training required to administer the medication (particularly in LMICs), it seems likely that the use of any additional uterotonics (in combination) would exacerbate these problems.

Ergometrine is contraindicated in severe hypertension and eclampsia, as there is a risk of hypertension associated with its use.

While both ergometrine and oxytocin are listed separately on the WHO Model List of Essential Medicines, a fixed-dose ergometrine/oxytocin combination medication is not listed *(18)*.

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 oxytocin plus ergometrine	— Favours oxytocin plus ergometrine
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 oxytocin plus ergometrine	— Favours oxytocin plus ergometrine
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: Oxytocin plus ergometrine
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 (Review). Cochrane Database Syst Rev. 2018:CD011689 *(2)*.

Outcome	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 oxytocin plus ergometrine	Risk difference with oxytocin plus ergometrine
Maternal death	Not reported	—	1.19 (0.17–8.43)[a]	⨁◯◯◯ VERY LOW	1.19 (0.17–8.43)	⨁◯◯◯ VERY LOW	1 per 1000	1 per 1000	0 fewer per 1000 (1 fewer to 7 more)
							1 per 1000 (for vaginal birth)	1 per 1000 (for vaginal birth)	0 fewer per 1000 (1 fewer to 7 more) (for vaginal birth)
							See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)	See comments[d] (for caesarean birth)
PPH ≥1000 ml	0.44 (0.18–1.05)	⨁◯◯◯ VERY LOW	0.50 (0.38–0.66)	⨁⨁⨁◯ MODERATE	0.49 (0.38–0.63)	⨁⨁⨁◯ MODERATE	27 per 1000	13 per 1000	14 fewer per 1000 (17 fewer to 10 fewer)
							27 per 1000 (for vaginal birth)	13 per 1000 (for vaginal birth)	14 fewer per 1000 (17 fewer to 10 fewer) (for vaginal birth)
							See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)	See comments[d] (for caesarean birth)
Blood transfusions	0.34 (0.18–0.66)	⨁⨁⨁◯ MODERATE	0.58 (0.35–0.98)	⨁⨁◯◯ LOW	0.46 (0.31–0.69)	⨁⨁⨁◯ MODERATE	27 per 1000	12 per 1000	15 fewer per 1000 (19 fewer to 8 fewer)
							27 per 1000 (for vaginal birth)	12 per 1000 (for vaginal birth)	15 fewer per 1000 (19 fewer to 8 fewer) (for vaginal birth)
							See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)	See comments[d] (for caesarean birth)

Outcome	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 oxytocin plus ergometrine	Risk difference with oxytocin plus ergometrine
Intensive care unit (ICU) admissions	Not reported	—	1.39 (0.08–22.64[a]	⨁◯◯◯ VERY LOW	1.39 (0.08–22.64)	⨁◯◯◯ VERY LOW	2 per 1000	3 per 1000	1 more per 1000 (2 fewer to 43 more)
							2 per 1000 (for vaginal birth)	3 per 1000 (for vaginal birth)	1 more per 1000 (2 fewer to 43 more) (for vaginal birth)
							See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)	See comments[d] (for caesarean birth)
Maternal shock	Not reported	—	—	—	—	—	—	—	—
PPH ≥ 500 ml	0.37 (0.30–0.46)	⨁⨁⨁◯ MODERATE	0.42 (0.33–0.55)	⨁⨁⨁◯ MODERATE	0.41 (0.33–0.51)	⨁⨁⨁◯ MODERATE	255 per 1000	105 per 1000	150 fewer per 1000 (171 fewer to 125 fewer)
							255 per 1000 (for vaginal birth)	105 per 1000 (for vaginal birth)	150 fewer per 1000 (171 fewer to 125 fewer) (for vaginal birth)
							320 per 1000 (for caesarean birth)	131 per 1000 (for caesarean birth)	189 fewer per 1000 (214 fewer to 157 fewer) (for caesarean birth)
Use of additional uterotonics	0.19 (0.15–0.24)	⨁⨁⨁◯ MODERATE	0.32 (0.22–0.47)	⨁◯◯◯ VERY LOW	0.28 (0.20–0.39)	⨁⨁◯◯ LOW	211 per 1000	59 per 1000	152 fewer per 1000 (169 fewer to 129 fewer)
							193 per 1000 (for vaginal birth)	54 per 1000 (for vaginal birth)	139 fewer per 1000 (154 fewer to 118 fewer) (for vaginal birth)
							746 per 1000 (for caesarean birth)	209 per 1000 (for caesarean birth)	537 fewer per 1000 (597 fewer to 455 fewer) (for caesarean birth)

Outcome	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 oxytocin plus ergometrine	Risk difference with oxytocin plus ergometrine
Mean blood loss (ml)	MD 35.02 ml lower (101.63 ml lower to 31.59 ml higher)	⨁◯◯◯ VERY LOW	MD 93.76 ml lower (147.66–39.86 ml lower)	⨁◯◯◯ VERY LOW	MD 82.24 ml lower (130.59–33.89 ml lower)	⨁⨁◯◯ LOW	The mean blood loss was 295 ml (range across placebo groups: 167.4–853.0 ml)	The mean blood loss with ergometrine plus oxytocin was on average 82.24 ml lower (range: 130.59 ml lower to 33.89 ml lower)	
							The mean blood loss for vaginal birth was 294 ml (range: 167.4–680 ml)	The mean blood loss with oxytocin plus ergometrine was on average 82.24 ml lower (range: 130.59 ml lower to 33.89 ml lower)	
							The mean blood loss for caesarean birth was 815 ml (range: 800–853 ml)	The mean blood loss with oxytocin plus ergometrine was on average 82.24 ml lower (range: 130.59 ml lower to 33.89 ml lower)	
Change in haemoglobin (Hb) (g/L)	MD 3.57 g/L lower (6.50–0.63 g/L lower)	⨁⨁◯◯ LOW	MD 3.09 g/L lower (5.34–0.84 g/L lower)	⨁◯◯◯ VERY LOW	MD 3.21 g/L lower (5.13–1.29 g/L lower)	⨁⨁◯◯ LOW	The mean change in Hb was 8.1 g/L (range: 6.0–13.5 g/L)	The mean change in Hb with oxytocin plus ergometrine was on average 3.21 g/L lower (range: 5.13 g/L lower to 1.29 g/L lower)	
							The mean change in Hb for vaginal birth was 8.1 g/L (range: 6.0–13.5 g/L)	The mean change in Hb with oxytocin plus ergometrine was on average 3.21 g/L lower (range: 5.13 g/L lower to 1.29 g/L lower)	
							The mean change in Hb for caesarean birth was 8.4 g/L	The mean change in Hb with oxytocin plus ergometrine was on average 3.21 g/L lower (range: 5.13 g/L lower to 1.29 g/L lower)	
Breastfeeding	1.03 (0.99–1.07)	⨁⨁⨁◯ MODERATE	0.98 (0.93–1.04)	⨁⨁⨁◯ MODERATE	1.01 (0.97–1.05)	⨁⨁⨁◯ MODERATE	746 per 1000	753 per 1000	7 more per 1000 (22 fewer to 37 more)
							746 per 1000 (for vaginal birth)	753 per 1000 (for vaginal birth)	7 more per 1000 (22 fewer to 37 more) (for vaginal birth)
							See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)	See comments[d] (for caesarean birth)
Nausea	1.95 (1.38–2.76)	⨁⨁⨁◯ MODERATE	1.72 (0.89–3.33)	⨁⨁◯◯ LOW	1.78 (1.04–3.08)	⨁⨁⨁◯ MODERATE	37 per 1000	66 per 1000	29 more per 1000 (1 more to 77 more)
							37 per 1000 (for vaginal birth)	66 per 1000 (for vaginal birth)	29 more per 1000 (1 more to 77 more) (for vaginal birth)
							67 per 1000 (for caesarean birth)	119 per 1000 (for caesarean birth)	52 more per 1000 (3 more to 139 more)

Outcome	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 oxytocin plus ergometrine	Risk difference with oxytocin plus ergometrine
Vomiting	2.15 (1.46–3.18)	⨁⨁⨁◯ MODERATE	3.66 (1.80–7.44)	⨁◯◯◯ VERY LOW	2.88 (1.73–4.78)	⨁⨁⨁◯ MODERATE	34 per 1000	98 per 1000	64 more per 1000 (25 more to 129 more)
							34 per 1000 (for vaginal birth)	98 per 1000 (for vaginal birth)	64 more per 1000 (25 more to 129 more) (for vaginal birth)
							See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)	See comments[d] (for caesarean birth)
Headache	1.65 (0.78–3.48)	⨁⨁◯◯ LOW	1.51 (0.60–3.82)	⨁⨁◯◯ LOW	1.57 (0.80–3.03)	⨁⨁◯◯ LOW	12 per 1000	19 per 1000	7 more per 1000 (2 fewer to 24 more)
							12 per 1000 (for vaginal birth)	19 per 1000 (for vaginal birth)	7 more per 1000 (2 fewer to 24 more) (for vaginal birth)
							See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)	See comments[d] (for caesarean birth)
Abdominal pain	Not reported	—	1.40 (0.83–2.36)[a]	⨁⨁⨁◯ MODERATE	1.40 (0.83–2.36	⨁⨁⨁◯ MODERATE	339 per 1000	475 per 1000	136 more per 1000 (58 fewer to 461 more)
							339 per 1000 (for vaginal birth)	475 per 1000 (for vaginal birth)	136 more per 1000 (58 fewer to 461 more) (for vaginal birth)
							See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)	See comments[d] (for caesarean birth)
Hypertension	Not reported	—	2.08 (0.25–17.16)[a]	⨁⨁◯◯ LOW	2.08 (0.25–17.16)	⨁⨁◯◯ LOW	7 per 1000	14 per 1000	7 more per 1000 (5 fewer to 112 more)
							7 per 1000 (for vaginal birth)	14 per 1000 (for vaginal birth)	7 more per 1000 (5 fewer to 112 more) (for vaginal birth)
							See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)	See comments[d] (for caesarean birth)

Outcome	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 oxytocin plus ergometrine	Risk difference with oxytocin plus ergometrine
Shivering	Not reported	—	0.96 (0.49–1.89)[a]	⨁⨁◯◯ LOW	0.96 (0.49–1.89)	⨁⨁◯◯ LOW	148 per 1000	142 per 1000	6 fewer per 1000 (75 fewer to 132 more)
							148 per 1000 (for vaginal birth)	142 per 1000 (for vaginal birth)	6 fewer per 1.000 (75 fewer to 132 more) (for vaginal birth)
							See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)	See comments[d] (for caesarean birth)
Fever	Not reported	—	0.74 (0.28–1.95)[a]	⨁⨁⨁◯ MODERATE	0.74 (0.28–1.95)	⨁⨁⨁◯ MODERATE	29 per 1000	21 per 1000	8 fewer per 1000 (21 fewer to 28 more)
							29 per 1000 (for vaginal birth)	23 per 1000 (for vaginal birth)	8 fewer per 1000 (21 fewer to 28 more) (for vaginal birth)
							See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)	See comments[d] (for caesarean birth)
Diarrhoea	Not reported	—	2.25 (0.89–5.71)[a]	⨁⨁◯◯ LOW	2.25 (0.89–5.71)	⨁⨁◯◯ LOW	6 per 1000	14 per 1000	8 more per 1000 (1 fewer to 28 more)
							6 per 1000 (for vaginal birth)	14 per 1000 (for vaginal birth)	8 more per 1000 (1 fewer to 28 more) (for vaginal birth)
							See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)	See comments[d] (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 plus ergometrine group (and their 95% CI) are based on the assumed risk in the placebo or no treatment group and the relative effect of oxytocin plus ergometrine (and its 95% CI) derived from the network meta-analysis.

[a] 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.

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

[c] Absolute risk with oxytocin cannot be estimated in the absence of absolute risk with placebo or no treatment.

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

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/

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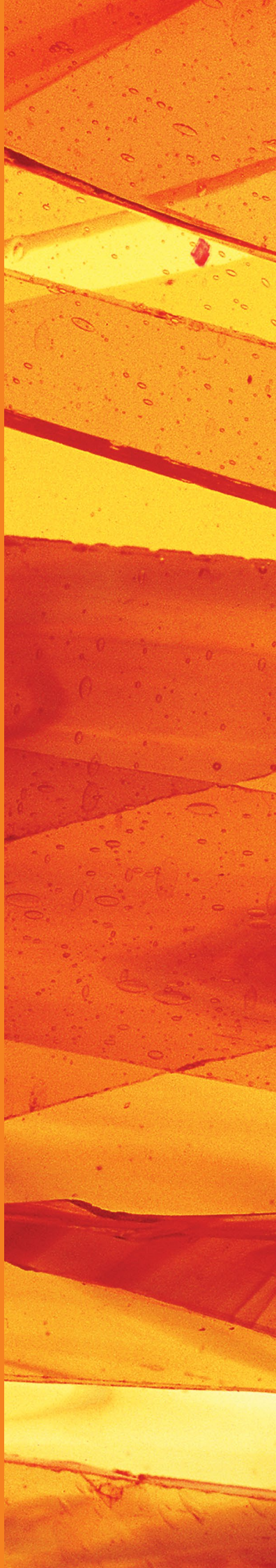

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