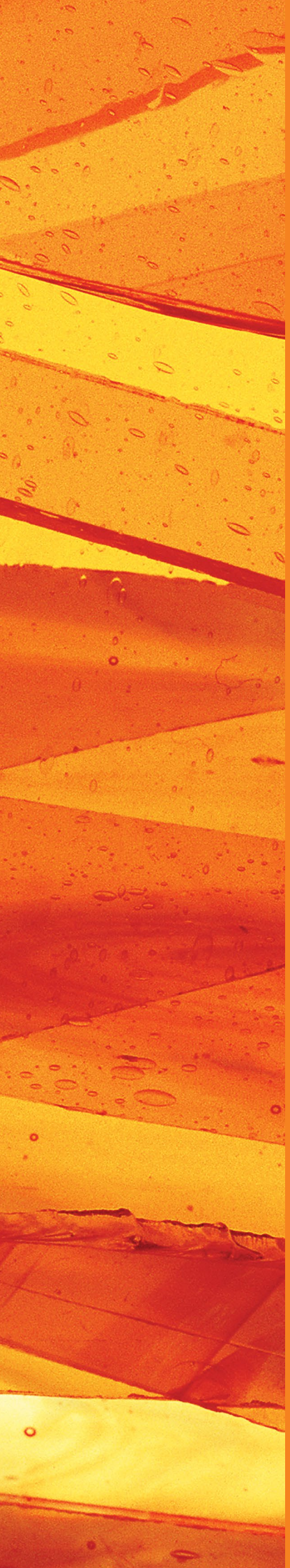

WHO recommendations

Uterotonics for the prevention of postpartum haemorrhage

Web annex 1: Oxytocin 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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Evidence to Decision framework

World Health Organization

WHO/RHR/18.28

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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

Oxytocin at low doses produces rhythmic uterine contractions that are indistinguishable in frequency, force and duration from those observed during spontaneous labour; at higher doses it can cause sustained uterine contractions.

It 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 by the intravenous (IV) route, oxytocin causes an almost immediate effect and reaches a peak concentration after 30 minutes, whereas intramuscular (IM) administration results in a slower onset of action, taking between 3 and 7 minutes, but produces a longer-lasting clinical effect of up to 1 hour.

Oxytocin is unstable in high ambient temperatures and requires a cold chain through storage and transport to prolong its shelf life.

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 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): Women in the third stage of labour

Intervention (I): Oxytocin

Comparator (C): Placebo or no treatment

Setting: Hospital or 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) admission
- Severe maternal morbidity: shock
- PPH ≥ 500ml
- Use of additional uterotonics
- Blood loss (ml)
- Postpartum anaemia

[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.

- Breastfeeding
- Side-effects[1]
- Maternal well-being
- Maternal satisfaction

3. Assessment

3.1 Effects of interventions

What is the effect of oxytocin 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 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.

Twelve randomized trials (9083 women) in the network meta-analysis directly compared oxytocin with placebo or no treatment. Nine of these trials were conducted in hospital settings, one in a community setting, and two included births in both

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

hospital and community settings. The trials were carried out in Egypt, France, Ghana, the Netherlands (three studies), Norway, Sweden (two studies), Tunisia and the United States of America (USA), and one study involved women in Egypt and South Africa. Most of these trials recruited only women with singleton pregnancies, but two trials (one in Ghana and the other in Egypt/South Africa) recruited women with either singleton or multiple pregnancies. Ten trials included only vaginal births, and two (in Norway and the USA) included only women undergoing caesarean section. The studies differed considerably in oxytocin dose and route of administration.

- One study used 2.5 international units (IU) IM.
- Four studies used 5 IU IM.
- Two studies used 10 IU IM.
- Two studies used a 5 IU via IV bolus.
- Two studies used 10 IU IV.
- One study administered doses ranging from 0.5 to 5 IU IV.

Effects of oxytocin 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: When compared with placebo or no treatment, low-certainty evidence suggests that oxytocin may make little or no difference to the risk of maternal death (risk ratio [RR] 1.60, 95% confidence interval [CI] 0.11–23.86).

PPH ≥ 1000 ml: High-certainty evidence suggests that oxytocin reduces PPH ≥ 1000 ml compared with placebo or no treatment (RR 0.59, 95% CI 0.50–0.70).

Blood transfusion: When compared with placebo or no treatment, moderate-certainty evidence suggests that prophylactic oxytocin probably reduces the use of blood transfusion (RR 0.60, 95% CI 0.41–0.87).

Severe maternal morbidity – ICU admission: Low-certainty evidence suggests that oxytocin may make little or no difference to ICU admissions, although this was a rare event in the study that reported it (RR 0.86, 95% CI 0.11–6.99). There were no data for the outcome "shock" reported in the included trials.

PPH ≥ 500 ml: Moderate-certainty evidence suggests that oxytocin probably reduces PPH ≥ 500 ml compared with placebo or no treatment (RR 0.58, 95% CI 0.49–0.70).

Use of additional uterotonics: When compared with placebo or no treatment, moderate-certainty evidence suggests that prophylactic oxytocin probably reduces the use of additional uterotonics (RR 0.42, 95% CI 0.3–0.56).

Mean blood loss: Low-certainty evidence suggests that blood loss may on average be slightly less among women receiving oxytocin compared with women receiving placebo or no treatment (mean difference [MD] 56.98 ml lower, 95% CI 98.15–15.82 ml lower).

Postpartum anaemia: This outcome was not directly reported in the review. However, there is moderate-certainty evidence to suggest that the **mean change in haemoglobin level** before versus after birth is probably slightly less among women receiving prophylactic oxytocin compared with those receiving placebo or no treatment (MD 2.14 g/L lower, 95% CI 3.87–0.41 g/L lower).

Breastfeeding: Moderate-certainty evidence suggests that oxytocin probably makes little or no difference to the proportion of women who are breastfeeding at the time of discharge from hospital (RR 1.02, 95% CI 0.98–1.06).

Any side-effect: Moderate-certainty evidence suggests that prophylactic oxytocin probably makes little or no difference to the risk of experiencing **nausea** (RR 0.88, 95% CI 0.53–1.49), **vomiting** (RR 0.98, 95% CI 0.58–1.66) or **abdominal pain** (RR 1.01, 95% CI 0.70–1.44). Low-certainty evidence suggests that prophylactic oxytocin may make little or no difference to the risk of **headache** (RR 1.45, 95% CI 0.74–2.81), **hypertension** (RR 0.84, 95% CI 0.11–6.57), **shivering** (RR 0.70, 95% CI 0.41–1.20), **fever** (RR 1.06, 95% CI 0.51–2.21) or **diarrhoea** (RR 1.25, 95% CI 0.51–3.07).

Maternal well-being: Only one trial from the direct comparison provided some evidence that may be relevant to this outcome. Low-certainty evidence suggests that the use of prophylactic oxytocin may make little or no difference to women's experience of less energy than before birth at three months postpartum (RR 1.02, 95% CI 0.93–1.13) or to experience of fatigue at three months postpartum (RR 0.99, 95% CI 0.95–1.04).

Maternal satisfaction: Only one trial from the direct comparison provided some evidence relating to this outcome. Moderate-certainty evidence suggests that the use of prophylactic oxytocin may make little or no difference to women's perception of whether management of the birth positively influenced their childbirth experience (RR 1.01, 95% CI 0.89–1.15), or made little or no difference to the maternal childbirth experience (RR 1.02, 95% CI 0.90–1.15). Low-certainty evidence suggests that the use of prophylactic oxytocin may make little or no difference to the extent to which women perceive that management of the birth negatively influenced their childbirth experience (RR 0.73, 95% CI 0.47–1.13).

Additional considerations

Subgroup analyses did not reveal a substantial difference in the effects of prophylactic oxytocin 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).

The results of a 2013 Cochrane review that specifically focused on the effects of prophylactic oxytocin versus placebo and other uterotonics were consistent with the above findings *(3)*. A separate 2016 Cochrane review assessed the effectiveness and safety of oxytocin provided in non-facility birth settings to women in the third stage of labour to prevent PPH *(4)*. The review authors identified a single cluster-randomized controlled trial, and concluded that it is uncertain if oxytocin administered by non-skilled birth attendants in non-facility birth settings (compared with a control group) reduces the incidence of severe PPH, severe maternal morbidity or maternal deaths. However, the intervention probably decreases PPH (≥ 500 ml).

Desirable effects

How substantial are the desirable anticipated effects of oxytocin 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 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 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 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*) *(5)*. 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*) *(6)*. 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 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 oxytocin 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	✓ Favours oxytocin

3.3 Resources

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

Research evidence

A systematic review of the literature found no direct evidence on the costs and cost–effectiveness of oxytocin to prevent PPH compared with no PPH prevention *(7)*. However, indirect evidence on cost–effectiveness of PPH prevention from studies of other uterotonics *(8–13)* suggests that oxytocin compared with no PPH prevention is probably cost–effective because the beneficial effects of oxytocin are substantial (e.g. as shown for "PPH ≥ 1000 ml" and "use of additional uterotonics"), with minimal side-effects. The resources required will vary according to whether the birth setting is in the hospital or in the community.

Additional considerations

- This indirect evidence on oxytocin cost–effectiveness would apply to both vaginal and caesarean section birth, as its effects are consistent for both modes of birth *(8–13)*.
- Oxytocin requires refrigerated storage and transport, which are not readily available in low-resource settings *(10)*.
- Concerns about the quality of oxytocin supplies *(10)* and wastage (due to heat compromise), expiry and Uniject device breakage *(14)* have been reported.
- Oxytocin was found to be the cheapest uterotonic agent in a cost–effectiveness review for the United Kingdom setting *(15)*.

Main resource requirements

Resource	Description
Staff	Oxytocin requires parenteral administration (IV or IM) by skilled health care personnel. Uniject devices (prefilled, easy-to-use, single-dose devices) can be used by community-level providers.
Training	Training to administer injections, and to monitor and manage expected and unexpected side-effects, is part of standard maternity staff training. However, additional training would be required if oxytocin is to be introduced in settings where it has not previously been available (e.g. if Uniject devices are to be used in a community setting).
Supplies	Oxytocin indicative cost: ■ Cost per 10 IU: US$ 0.22 – 1.19 *(10,15)* ■ Cost per Uniject device: US$ 1.25 *(16)*. Other costs: ■ Needle and syringe cost: approximately US$ 0.07 *(10)*.
Equipment and infrastructure	Cold chain storage and transport costs: Cost per birth: possibly US$ 0.84 in a low-resource setting *(13)*.
Time	IM administration takes 2 minutes (might be slightly quicker with Uniject); IV administration takes longer, if an IV cannula needs to be put in place for this purpose *(17)*.
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 the 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	— Favours oxytocin

3.4 Equity

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

Research evidence

Oxytocin, in injectable form, is relatively inexpensive and is already widely available in a range of resource settings (low to high). However, 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 the medication may limit its use in low-resource settings in LMICs, particularly in isolated rural areas where the need is arguably greatest (*moderate confidence*) *(6)*. 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 *(18)*. 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. The availability of Uniject has the potential to increase coverage beyond hospital settings without compromising efficacy and safety for disadvantaged women.

Judgement

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

3.5 Acceptability

Is 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 indicate that providers recognize the benefits of using oxytocin to prevent PPH and hasten the delivery of the placenta (*moderate confidence*) *(6)*. However, in some LMIC settings, providers hold the perception that the medication may cause retained placenta when administered preventatively or may 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*) *(6)*.

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

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".

Judgement

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

3.6 Feasibility

Is oxytocin for PPH prevention feasible to implement?

Research evidence

Findings from a qualitative systematic review exploring perceptions of PPH prevention and treatment among women and health care providers suggest that resource constraints may influence effective use of oxytocin for PPH prevention, particularly in LMICs (*high confidence*) *(6)*. Inconsistent supplies and concerns 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 a wide variety of settings, health care providers feel they need more training in PPH management or training on when/how to administer oxytocin (*high confidence*). In areas where task shifting has 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*) *(6)*.

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

Additional considerations

Injectable oxytocin is already widely available in a range of resource settings (low to high) and has multiple applications (such as for PPH prevention and treatment as well as labour induction). Oxytocin (10 IU in 1 ml for injection) is listed in the WHO Model List of Essential Medicines *(20)*.

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.

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	✓ Favours oxytocin
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	— Favours oxytocin
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 ☐ in specific contexts ☐ with targeted monitoring and evaluation ☐ in the context of rigorous research	We recommend the intervention ☑

5. Summary of Findings table

Patient or population: Women in the third stage of labour
Setting: Hospital or community setting
Intervention: Oxytocin
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)*.

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 oxytocin	Risk difference with oxytocin
Maternal death	Not estimable	⨁◯◯◯ VERY LOW	1.60 (0.11–23.86)[a]	⨁⨁◯◯ LOW	1.60 (0.11–23.86)	⨁⨁◯◯ LOW	1 per 1000	2 per 1000	1 more per 1000 (1 fewer to 23 more)
							1 per 1000 (for vaginal birth)	2 per 1000 (for vaginal birth)	1 more per 1000 (1 fewer to 23 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	0.61 (0.52–0.73)	⨁⨁⨁◯ MODERATE	0.56 (0.42–0.75)	⨁⨁⨁⨁ HIGH	0.59 (0.50–0.70)	⨁⨁⨁⨁ HIGH	27 per 1000	16 per 1000	11 fewer per 1000 (14 fewer to 8 fewer)
							27 per 1000 (for vaginal birth)	16 per 1000 (for vaginal birth)	11 fewer per 1000 (14 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)
Blood transfusion	0.75 (0.51–1.12)	⨁⨁◯◯ LOW	0.42 (0.23–0.75)	⨁⨁⨁◯ MODERATE	0.60 (0.41–0.87)	⨁⨁⨁◯ MODERATE	27 per 1000	16 per 1000	11 fewer per 1000 (16 fewer to 4 fewer)
							27 per 1000 (for vaginal birth)	16 per 1000 (for vaginal birth)	11 fewer per 1000 (16 fewer to 4 fewer) (for vaginal birth)
							See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)	See comments[d] (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 oxytocin	Risk difference with oxytocin
Intensive care unit (ICU) admission	Not estimable	⨁◯◯◯ VERY LOW	0.86 (0.11–6.99)a	⨁⨁◯◯ LOW	0.86 (0.11–6.99)	⨁⨁◯◯ LOW	2 per 1000	2 per 1000	0 fewer per 1000 (2 fewer to 12 more)
							2 per 1000 (for vaginal birth)	2 per 1000 (for vaginal birth)	0 fewer per 1000 (2 fewer to 12 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 ≥ 500ml	0.61 (0.52–0.71)	⨁⨁⨁◯ MODERATE	0.57 (0.43–0.74)	⨁⨁◯◯ LOW	0.58 (0.49–0.70)	⨁⨁⨁◯ MODERATE	255 per 1000	148 per 1000	107 fewer per 1000 (130–77 fewer)
							255 per 1000 (for vaginal birth)	148 per 1000 (for vaginal birth)	107 fewer per 1000 (130 fewer to 77 fewer) (for vaginal birth)
							320 per 1000 (for caesarean birth)	186 per 1000 (for caesarean birth)	134 fewer per 1000 (163 fewer to 96 fewer) (for vaginal birth)
Use of additional uterotonics	0.43 (0.32–0.58)	⨁⨁⨁◯ MODERATE	0.43 (0.29–0.63)	⨁⨁◯◯ LOW	0.42 (0.32–0.56)	⨁⨁⨁◯ MODERATE	211 per 1000	89 per 1000	122 fewer per 1000 (150 fewer to 78 fewer)
							193 per 1000 (for vaginal birth)	81 per 1000 (for vaginal birth)	112 fewer per 1000 (137 fewer to 71 fewer) (for vaginal birth)
							746 per 1000 (for caesarean birth)	313 per 1000 (for caesarean birth)	433 fewer per 1000 (530 fewer to 276 fewer) (for vaginal 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 oxytocin	Risk difference with oxytocin
Mean blood loss (ml)	MD 118.52 lower (141.40 lower to 95.64 lower)	⨁⨁⨁◯ MODERATE	MD 27.19 lower (79.51 lower to 25.14 higher)	⨁◯◯◯ VERY LOW	MD 56.98 lower (98.15 lower to 15.82 lower)	⨁⨁◯◯ LOW	The mean blood loss was 295 ml (range across placebo groups: 167.4–853.0 ml)	The mean blood loss with oxytocin was on average 56.98 lower (range: 98.15 lower to 15.82 lower)	
							The mean blood loss for vaginal birth was 294 ml (range: 167.4–680.0 ml)	The mean blood loss with oxytocin was on average 56.98 lower (range: 98.15 lower to 15.82 lower)	
							The mean blood loss for caesarean birth was 815 ml (range: 800–853.0 ml)	The mean blood loss with oxytocin was on average 56.98 lower (range: 98.15 lower to 15.82 lower)	
Change in haemoglobin (Hb) (g/L)	MD 2.68 lower (4.47 lower to 0.89 lower)	⨁⨁⨁◯ MODERATE	MD 1.68 lower (3.99 lower to 0.62 higher)	⨁◯◯◯ VERY LOW	MD 2.14 lower (3.87 lower to 0.41 lower)	⨁⨁⨁◯ MODERATE	The mean change in Hb was 8.1 g/L (range: 6.0–13.5 g/L)	The mean change in Hb with oxytocin was on average 2.14 lower (range: 3.87 lower to 0.41 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 was on average 2.14 lower (range: 3.87 lower to 0.41 lower)	
							The mean change in Hb for caesarean was 8.4 g/L	The mean change in Hb with oxytocin was on average 2.14 lower (range: 3.87 lower to 0.41 lower)	
Breastfeeding	1.00 (0.95–1.05)	⨁⨁⨁◯ MODERATE	1.04 (0.99–1.09)	⨁⨁⨁◯ MODERATE	1.02 (0.98–1.06)	⨁⨁⨁◯ MODERATE	746 per 1000	761 per 1000	15 more per 1000 (15 fewer to 45 more)
							746 per 1000 (for vaginal birth)	761 per 1000 (for vaginal birth)	15 more per 1000 (15 fewer to 45 more)
							See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)	See comments[d] (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 oxytocin	Risk difference with oxytocin
Nausea	0.82 (0.47–1.42)	⨁⨁◯◯ LOW	0.98 (0.53–1.83)	⨁⨁⨁◯ MODERATE	0.88 (0.53–1.49)	⨁⨁⨁◯ MODERATE	37 per 1000	33 per 1000	4 fewer per 1000 (17 fewer to 18 more)
							37 per 1000 (for vaginal birth)	33 per 1000 (for vaginal birth)	4 fewer per 1000 (17 fewer to 18 more) (for vaginal birth)
							67 per 1000 (for caesarean birth)	59 per 1000 (for caesarean birth)	8 fewer per 1000 (31 fewer to 31 more)
Vomiting	1.40 (0.44–4.41)	⨁◯◯◯ VERY LOW	0.93 (0.53–1.64)	⨁⨁⨁◯ MODERATE	0.98 (0.58–1.66)	⨁⨁⨁◯ MODERATE	34 per 1000	33 per 1000	1 fewer per 1000 (14 fewer to 22 more)
							34 per 1000 (for vaginal birth)	33 per 1000 (for vaginal birth)	1 fewer per 1000 (14 fewer to 22 more) (for vaginal birth)
							See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)	See comments[d] (for caesarean birth)
Headache	1.56 (0.52–4.74)	⨁⨁◯◯ LOW	1.40 (0.59–3.31)	⨁⨁◯◯ LOW	1.45 (0.74–2.81)	⨁⨁◯◯ LOW	12 per 1000	17 per 1000	5 more per 1000 (3 fewer to 22 more)
							12 per 1000 (for vaginal birth)	17 per 1000 (for vaginal birth)	5 more per 1000 (3 fewer to 22 more)
							See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)	See comments[d] (for caesarean birth)
Abdominal pain	0.89 (0.80–1.00)	⨁⨁⨁◯ MODERATE	1.21 (0.68–2.27)	⨁⨁⨁◯ MODERATE	1.01 (0.70–1.44)	⨁⨁⨁◯ MODERATE	339 per 1000	339 per 1000	3 more per 1000 (102 fewer to 149 more)
							339 per 1000 (for vaginal birth)	339 per 1000 (for vaginal birth)	3 more per 1000 (102 fewer to 149 more) (for vaginal birth)
							See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)	See comments[d] (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 oxytocin	Risk difference with oxytocin
Hypertension	Not reported	—	0.84 (0.11–6.57)a	⨁⨁◯◯ LOW	0.84 (0.11–6.57)	⨁⨁◯◯ LOW	7 per 1000	6 per 1000	1 fewer per 1000 (6 fewer to 38 more)
							7 per 1000 (for vaginal birth)	6 per 1000 (for vaginal birth)	1 fewer per 1000 (6 fewer to 38 more)
							See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)	See comments[d] (for caesarean birth)
Shivering	Not estimable	⨁◯◯◯ VERY LOW	0.70 (0.41–1.20)a	⨁⨁◯◯ LOW	0.70 (0.41–1.20)	⨁⨁◯◯ LOW	148 per 1000	102 per 1000	44 fewer per 1000 (87 fewer to 30 more)
							148 per 1000 (for vaginal birth)	102 per 1000 (for vaginal birth)	44 fewer per 1000 (87 fewer to 30 more) (for vaginal birth)
							See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)	See comments[d] (for caesarean birth)
Fever	Not estimable	⨁◯◯◯ VERY LOW	1.06 (0.51–2.21)a	⨁⨁◯◯ LOW	1.06 (0.51–2.21)	⨁⨁◯◯ LOW	29 per 1000	31 per 1000	2 more per 1000 (14 fewer to 35 more)
							29 per 1000 (for vaginal birth)	31 per 1000 (for vaginal birth)	2 more per 1000 (14 fewer to 35 more)
							See comments[b] (for caesarean birth)	See comments[c] (for caesarean birth)	See comments[d] (for caesarean birth)
Diarrhoea	Not reported	—	1.25 (0.51–3.07)a	⨁⨁◯◯ LOW	1.25 (0.51–3.07)	⨁⨁◯◯ LOW	6 per 1000	8 per 1000	2 more per 1000 (3 fewer to 12 more)
							6 per 1000 (for vaginal birth)	8 per 1000 (for vaginal birth)	2 more per 1000 (3 fewer to 12 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 groups group are based on weighted means of baseline risks from the studies with placebo groups in the network meta-analysis. The corresponding risks in the oxytocin group (and their 95% CI) 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] 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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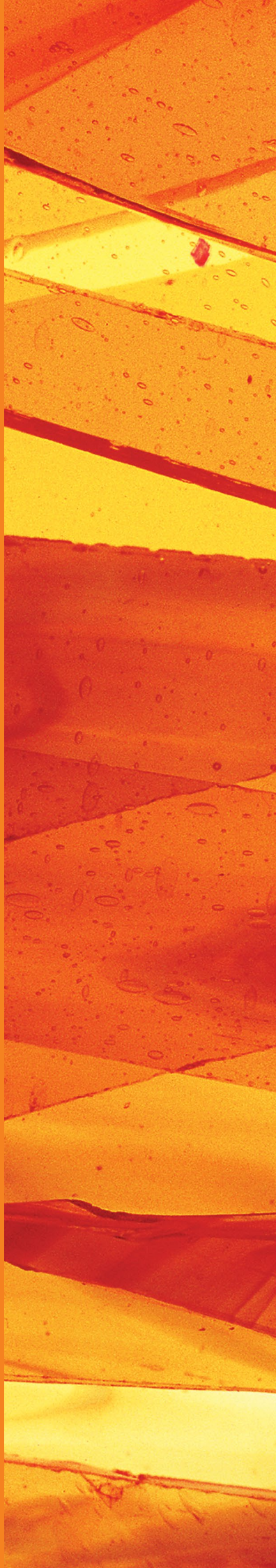

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