Intravenous versus intramuscular prophylactic oxytocin for the third stage of labour (Review)

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[Intervention Review]

Intravenous versus intramuscular prophylactic oxytocin for the third stage of labour

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ABSTRACT

Background

There is general agreement that oxytocin given either through the intravenous or intramuscular route is effective in reducing postpartum blood loss. However, it is unclear whether the subtle differences between the mode of action of these routes have any effect on maternal and infant outcomes. This review was first published in 2012 and last updated in 2018.

Objectives

To determine the comparative effectiveness and safety of oxytocin administered intravenously or intramuscularly for prophylactic management of the third stage of labour after vaginal birth.

Search methods

We searched Cochrane Pregnancy and Childbirth's Trials Register, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) (19 December 2019), and reference lists of retrieved studies.

Selection criteria

Eligible studies were randomised trials comparing intravenous with intramuscular oxytocin for prophylactic management of the third stage of labour after vaginal birth. We excluded quasi-randomised trials.

Data collection and analysis

Two review authors independently assessed studies for inclusion and risk of bias, extracted data and checked them for accuracy. We assessed the certainty of the evidence with the GRADE approach.

Main results

Seven trials, involving 7817 women, met the inclusion criteria for this review. The trials compared intravenous versus intramuscular administration of oxytocin just after the birth of the anterior shoulder or soon after the birth of the baby. All trials were conducted in hospital settings and included women with term pregnancies, undergoing a vaginal birth. Overall, the included studies were at moderate or low risk of bias, with two trials providing clear information on allocation concealment and blinding. For GRADE outcomes, the certainty of the evidence was generally moderate to high, except from two cases where the certainty of the evidence was either low or very low.

High-certainty evidence suggests that intravenous administration of oxytocin in the third stage of labour compared with intramuscular administration carries a lower risk for postpartum haemorrhage (PPH) ≥ 500 mL (average risk ratio (RR) 0.78, 95% confidence interval (CI) 0.66 to 0.92; six trials; 7731 women) and blood transfusion (average RR 0.44, 95% CI 0.26 to 0.77; four trials; 6684 women). Intravenous administration of oxytocin probably reduces the risk of PPH ≥ 1000 mL, although the 95% CI crosses the line of no-effect (average RR 0.65, 95% CI 0.39 to 1.08; four trials; 6681 women; moderate-certainty evidence). In all studies but one, there was a reduction in the risk of PPH ≥ 1000 mL with intravenous oxytocin. The study that found a large increase with intravenous administration was small (256 women), and contributed only 3% of total events. Once this small study was removed from the meta-analysis, heterogeneity was eliminated and the treatment effect favoured intravenous oxytocin (average RR 0.61, 95% CI 0.42 to 0.88; three trials; 6425 women; high-certainty evidence). Additionally, a sensitivity analysis, exploring the effect of risk of bias by restricting analysis to those studies rated as 'low risk of bias' for random sequence generation and allocation concealment, found that the prophylactic administration of intravenous oxytocin reduces the risk for PPH ≥ 1000 mL, compared with intramuscular oxytocin (average RR 0.64, 95% CI 0.43 to 0.94; two trials; 1512 women). The two routes of oxytocin administration may be comparable in terms of additional uterotonic use (average RR 0.78, 95% CI 0.49 to 1.25; six trials; 7327 women; low-certainty evidence). Although intravenous compared with intramuscular administration of oxytocin probably results in a lower risk for serious maternal morbidity (e.g. hysterectomy, organ failure, coma, intensive care unit admissions), the confidence interval suggests a substantial reduction, but also touches the line of no-effect. This suggests that there may be no reduction in serious maternal morbidity (average RR 0.47, 95% CI 0.22 to 1.00; four trials; 7028 women; moderate-certainty evidence). Most events occurred in one study from Ireland reporting high dependency unit admissions, whereas in the remaining three studies there was only one case of uvular oedema. There were no maternal deaths reported in any of the included studies (very low-certainty evidence).

There is probably little or no difference in the risk of hypotension between intravenous and intramuscular administration of oxytocin (RR 1.01, 95% CI 0.88 to 1.15; four trials; 6468 women; moderate-certainty evidence).

Subgroup analyses based on the mode of administration of intravenous oxytocin (bolus injection or infusion) versus intramuscular oxytocin did not show any substantial differences on the primary outcomes. Similarly, additional subgroup analyses based on whether oxytocin was used alone or as part of active management of the third stage of labour (AMTSL) did not show any substantial differences between the two routes of administration.

Authors' conclusions

Intravenous administration of oxytocin is more effective than its intramuscular administration in preventing PPH during vaginal birth. Intravenous oxytocin administration presents no additional safety concerns and has a comparable side effects profile with its intramuscular administration. Future studies should consider the acceptability, feasibility and resource use for the intervention, especially in low-resource settings.

PLAIN LANGUAGE SUMMARY

Oxytocin injected into a vein or muscle for reducing blood loss after vaginal birth

We set out to look for evidence from randomised controlled trials on the effectiveness and safety of oxytocin injected into a vein, compared with injection into muscle, to prevent excessive bleeding immediately after vaginal birth.

What is the issue?

Most maternal deaths occur within the first 24 hours after delivery. Up to one-fourth of them are caused by excessive bleeding (called postpartum haemorrhage). In low-income countries, drugs to prevent or treat postpartum haemorrhage (uterotonics) are not always available. Oxytocin is one such drug. Oxytocin prevents excessive postpartum bleeding by helping the uterus to contract. It is given to the mother by injection into a vein or into muscle during or immediately after the birth of her baby.

Why is this important?

Blood loss after the birth of the baby depends on how quickly the placenta separates from the uterus and how well the uterus contracts to close the blood vessels that carried blood to the placenta.

Oxytocin given directly into a vein has an almost immediate effect which lasts for a relatively short time. When injected into muscle, oxytocin takes a few minutes to act, but the effect is longer-lasting. Giving injections into a vein requires special skills and sterile equipment that may not always be available. In contrast, injection into muscle is quick and requires relatively less skill.

Oxytocin injected into a vein may sometimes cause serious side effects, such as a sudden drop in blood pressure, especially when given rapidly in a small amount of solution (undiluted).

What evidence did we find?

We searched for evidence from randomised controlled trials on 19 December 2019 and identified seven studies (involving 7817 women). The studies compared oxytocin injected into a vein with injection into muscle during or immediately after the vaginal birth of the baby. All studies were conducted in hospitals and mostly recruited women giving birth vaginally to one baby at term. In all but two studies, both

women and hospital staff were aware of how the oxytocin was given. This may have had an impact on results. Overall, the included studies were at moderate or low risk of bias, and the certainty of the generated evidence was generally moderate to high.

We found that women receiving oxytocin through a vein were at lower risk for blood loss of 500 mL or more (six trials; 7731 women) and blood transfusion (four trials; 6684 women) compared with women receiving oxytocin into muscle. There was high-certainty evidence for both of these outcomes. The administration of oxytocin through a vein probably reduced the risk for severe blood loss of 1000 mL or more, compared with oxytocin into muscle (four trials; 6681 women; moderate-certainty evidence). The two highest-quality studies (1512 women) found that oxytocin injection into a vein reduced the risk for blood loss of 1000 mL or more, compared with oxytocin injection into muscle. Although the two ways of giving oxytocin may have been similar in terms of women requiring additional medications to contract the uterus, we have little confidence in these results (six trials; 7327 women; low-certainty evidence). Both routes of oxytocin were safe with probably same number of women experiencing side effects, including low blood pressure (four trials; 6468 women; moderate-certainty evidence). Probably fewer women receiving oxytocin through a vein experienced serious complications related to excessive bleeding, such as admission to intensive care, loss of consciousness, or organ failure (four trials; 7028 women; moderate-certainty evidence). No mother died in any of the included studies.

The studies did not report on women's and health personnel's satisfaction with either route of oxytocin administration.

What does this mean?

Oxytocin is more effective when given through a vein than oxytocin injected into muscle for preventing excessive bleeding soon after vaginal birth. Giving oxytocin into a vein did not cause additional safety concerns and had similar side effects compared with oxytocin injected into muscle. Future studies need to consider the acceptability of the two different ways of giving oxytocin to women and healthcare providers as important study outcomes. It is also important to investigate whether the benefits of giving oxytocin into a vein outweigh the higher cost.

Summary of findings 1. Intravenous compared to intramuscular oxytocin for PPH prevention

Intravenous (IV) compared to intramuscular (IM) prophylactic oxytocin in the 3rd stage of labour

Patient or population: women in the 3rd stage of labour undergoing a vaginal birth.
Setting: hospital
Intervention: intravenous (bolus or infusion) prophylactic oxytocin in the 3rd stage of labour
Comparison (reference): intramuscular prophylactic oxytocin in the 3rd stage of labour

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with IM prophylactic oxytocin in the 3rd stage of labour	Risk with IV				
Severe PPH ≥ 1000 mL	Study population		Average RR 0.65 (0.39 to 1.08)	6681 women (4 RCT)	⊕⊕⊕⊖ MODERATE[a]	-
	23 per 1000	15 per 1000 (9 to 25)				
Serious maternal morbidity	Study population		Average RR 0.47 (0.22 to 1.00)	7028 women (4 RCT)	⊕⊕⊕⊖ MODERATE[a]	2 of the included trials (5393 women) reported zero events.
	6 per 1000	3 per 1000 (1 to 6)				
Maternal death	Study population		Not estimable	7028 women (4 RCT)	⊕⊖⊖⊖ VERY LOW[b]	All 4 trials reported zero events.
	See comment	See comment				
PPH ≥ 500 mL	Study population		Average RR 0.78 (0.66 to 0.92)	7731 women (6 RCT)	⊕⊕⊕⊕ HIGH	-
	72 per 1000	56 per 1000 (48 to 66)				
Use of additional uterotonics	Study population		Average RR 0.78 (0.49 to 1.25)	7327 women (6 RCT)	⊕⊕⊖⊖ LOW[c]	-
	62 per 1000	49 per 1000				

		(31 to 78)				
Blood transfusion	Study population		Average RR 0.44 (0.26 to 0.77)	6684 women (4 RCT)	⊕⊕⊕⊕ HIGH	-
	13 per 1000	6 per 1000 (3 to 10)				
Hypotension	Study population		Average RR 1.01 (0.88 to 1.15)	6468 women (4 RCT)	⊕⊕⊕⊖ MODERATE[d]	-
	111 per 1000	112 per 1000 (98 to 128)				

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

CI: confidence interval; **PPH**: postpartum haemorrhage; **RCT**: randomised controlled trial; **RR:** risk ratio

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

[a]Evidence certainty downgraded -1 due to serious imprecision (wide 95% CI crossing the line of no-effect).
[b]Evidence certainty downgraded -1 due to serious limitations in study design (unclear risk for allocation concealment) and -2 due to very serious imprecision (lack of events).
[c]Evidence certainty downgraded -1 due to serious imprecision (wide 95% CI crossing the line of no-effect) and -1 due to serious inconsistency (I^2 = 61%).
[d]Evidence certainty downgraded -1 due to serious limitations in study design (unclear risk for allocation concealment and assessor blinding, lack of blinding of participants and personnel).

BACKGROUND

Recent global estimates of maternal mortality indicate that over 295,000 women, mostly from low-income countries, lost their lives during pregnancy and childbirth in 2017 (WHO 2019). It is well known that most deaths occur within the first 24 hours after delivery and up to one-fourth of these deaths can be attributed to postpartum haemorrhage (PPH) (Say 2014). Even when mothers survive excessive bleeding, they may undergo hysterectomy or other life-saving procedures that have important implications for future reproduction and quality of life (Carroll 2016; Souza 2013).

Description of the condition

The third stage of labour refers to the period between the birth of the baby and complete expulsion of the placenta and membranes. Blood loss during this period and immediately thereafter depends on how quickly the placenta separates from the uterine wall and how well the uterus contracts to close the vascular channels in the placenta bed. While this process is entirely physiologic and often results in moderate blood loss, in situations where the uterus fails to properly contract after childbirth (uterine atony), severe postpartum bleeding could put the mother at risk of dying. For centuries, failure of the uterus to contract and retract has been recognised as a major cause of PPH, and in spite of the presence of effective medical interventions, remains an important cause of maternal death (Oladapo 2016). Most PPH deaths occur in low-income countries, where a lack of access to uterotonic drug therapies combined with a high incidence of anaemia in pregnant women complicates the third stage of labour (Lazarus 2005).

According to the World Health Organization (WHO), PPH is defined as bleeding from the genital tract in excess of 500 mL after the birth of the baby (WHO 2018). Globally, this complication occurs in approximately 6% of all births although the prevalence is disproportionately higher in low-income countries (Carroli 2008). An evidence-based intervention that is universally recommended to reduce the incidence of PPH is the active management of the third stage of labour (FIGO 2012; NICE 2014; WHO 2012; WHO 2017). Active management of the third stage of labour is a set of interlocking interventions that usually include administration of a prophylactic uterotonic (preferably oxytocin) during or immediately after the birth of the baby, cord clamping and cutting, and placental delivery by controlled cord traction (WHO 2017). Compared with expectant management, active management significantly reduced the risk of PPH and severe PPH by 66%, maternal postpartum anaemia by 50%, blood transfusion by 65% and use of therapeutic uterotonics by 81% (Begley 2019). However, these benefits were achieved at the expense of an increased risk of maternal postnatal hypertension, need for opiate analgesia and afterpains. When the individual components of active management of the third stage of labour were separately analyzed, it was evident that the beneficial and adverse effects observed were mainly due to the uterotonic administered during the third stage of labour (Prendiville 2000).

Description of the intervention

Historically, the first uterotonic drugs were ergot alkaloids followed by oxytocin and finally prostaglandins. Of these three, oxytocin is the most widely used in clinical practice. Oxytocin is a 9-amino-acid peptide that is secreted in vivo by the posterior pituitary gland. It was first discovered in 1909 by Sir Henry Dale (Dale 1909), later synthesised in 1954 by du Vigneaud (Du Vigneaud 1954), and since then has been used for labour induction and augmentation and management of the third stage of labour. Oxytocin binds to its receptors in the smooth muscles of the uterus to cause rhythmic contractions of the upper uterine segment, more powerfully towards the end of pregnancy, during labour and immediately postpartum. It is not bound to plasma proteins and has a short circulating half-life of about three to five minutes. Oxytocin is deactivated in the gastrointestinal tract and thus its main route of administration is parenteral. The dose used for PPH prophylaxis varies widely between practitioners and obstetric units, ranging from 2 IU to 10 IU for both intravenous bolus and intramuscular injections. For intravenous infusion, the usual prophylactic dose is 20 IU in 500 mL of crystalloid solution, with the dosage rate adjusted according to response (Breathnach 2006). When given by the intravenous route, oxytocin causes an almost immediate action and reaches a plateau concentration after 30 minutes, whereas intramuscular administration results in a slower onset of action, taking between three and seven minutes, but produces a longer-lasting clinical effect of up to one hour (Breathnach 2006). Its elimination from the plasma is mainly through the liver and kidneys, with less than 1% excreted unchanged in the urine.

Oxytocin is stable at temperatures up to 25°C, but requires refrigeration to prolong its shelf life. This requirement constitutes a major challenge to ensure its potency in low-resource settings, where prolonged storage is common and the necessary facilities are either not available or in short supply. An important limitation of oxytocin is its short half-life, which makes repeated administration inevitable in certain situations. This limitation has led to the exploration of its long-acting analogue, carbetocin, which produces sustained uterine contractions similar to ergometrine but without its associated side effects (Gallos 2018; Su 2012).

How the intervention might work

Effectiveness in third stage of labour

For many years, oxytocin has remained a frontline uterotonic that plays a central role in the prevention of PPH. Even in the absence of active management of the third stage of labour, oxytocin alone reduces the incidence of PPH (WHO 2012). Today several uterotonics are recommended for PPH prophylaxis, including carbetocin, misoprostol, ergometrine, and Syntometrine®, but oxytocin is still the preferred choice, because it has similar efficacy, fewer side effects, no major contraindications, and is inexpensive, compared with other available options (WHO 2018). However, one limitation to its universal use for all women giving birth is that it requires parenteral administration and is thus restricted to settings where sterile equipment and providers skilled in injection practices and safety are available (WHO 2018). It is not a surprise though that in low-resource settings nearly one third of injections is performed with the use of inadequate equipment (Hutin 2003).

Since the aim of giving a prophylactic uterotonic is to hasten placental separation by stimulating uterine contractions soon after birth, it can be reasonably assumed that the sooner the onset of action of a uterotonic, the faster the placenta separates and the smaller the amount of blood loss. This assumption underlies the advice to give prophylactic uterotonic during the second stage of labour (either with crowning of the fetal head or delivery of its anterior shoulder) to allow time for prompt drug action as soon as the baby is born. While it is scientifically plausible for

the intravenous route to have a comparative advantage over the intramuscular route in this regard, this theory is not supported by evidence from a Cochrane Review comparing different timing of administration of uterotonics in active management of the third stage of labour (Soltani 2010). Administration of oxytocin before and after the expulsion of the placenta did not have any significant influence on many clinically important outcomes, such as the incidence of PPH and severe PPH, retained placenta, pre- and post-delivery changes in haemoglobin (Hb), the need for blood transfusion, use of additional uterotonic drugs and duration of the third stage of labour (Soltani 2010). This implies that a short delay in the onset of action of a uterotonic, as expected with intramuscular oxytocin, may not alter the outcomes related to blood loss when given for prophylaxis.

Potential adverse effects

Oxytocin is a vasoactive peptide with a complex hormonal activity. Apart from the uterine smooth muscles, specific receptors of oxytocin have been described in all kinds of tissues including the myocardium (heart muscle), vessels, central nervous systems and the breasts. Oxytocin shares about 5% of the antidiuretic properties of vasopressin as a result of certain similarities in their structures. This antidiuretic effect is responsible for the water intoxication that results from repeated administration of oxytocin in large volumes of electrolyte-free solutions. Depending on the degree of water overload, a woman could present with headaches, vomiting, drowsiness, confusion, lethargy, convulsions or coma (In 2011). It also has a direct relaxing effect on vascular smooth muscle leading to a decreased systemic vascular resistance, hypotension and tachycardia (rapid heart beat). These haemodynamic responses were mainly associated with the intravenous route of administration particularly when given by a rapid bolus injection, and often in women under anaesthesia for caesarean delivery or other pregnancy-related indications (Hendricks 1970; Langesaeter 2009; Pinder 2002; Secher 1978; Spence 2002; Thomas 2007; Weis 1975). Oxytocin administered as an intravenous bolus of 10 IU was reported to induce chest pain, transient profound tachycardia, hypotension and ECG changes suggestive of myocardial ischaemia (Charbit 2004; Svanström 2008). In the report, *Confidential enquiries into maternal deaths, 1997-1999* (Cooper 2002), the death of two mothers with cardiovascular instability was related to cardiac arrest following intravenous injection of 10 IU of oxytocin. This finding subsequently reinforced the recommendation of 5 IU of oxytocin for the third stage of labour, to be administered slowly or by controlled intravenous infusion, and since then has changed the practice in the UK (Bolton 2003). There are also reports to suggest that even low-dose oxytocin is not haemodynamically inert as a bolus injection of 5 IU has the potential to cause a marked but short-lived hypotension and tachycardia (Thomas 2007). These concerns have led to a call for caution in using intravenous oxytocin in women with unstable cardiovascular conditions, such as hypovolaemia, shock or cardiac disease.

Unlike intravenous oxytocin, there is a paucity of data regarding the side effects of intramuscular oxytocin probably because there are few of clinical importance. However, the usual side effects of any intramuscular injection, such as pain at injection site and injection abscess where safety procedures are not followed, are to be expected. The relative safety of intramuscular oxytocin, as perceived by stakeholders, is evident in the recommendations regarding prophylactic oxytocin by the International Federation of Obstetrics and Gynaecology (FIGO 2012), the National Institute for Clinical Excellence (NICE 2014), and the WHO (WHO 2012; WHO 2017), which are all in favour of the intramuscular route of administration.

Why it is important to do this review

While the efficacy of parenteral oxytocin in the prophylactic management of the third stage of labour is not being contested, there seems to be a general preference for the intramuscular route. Obstetric texts advocate the use of oxytocin, either intramuscularly or by dilute intravenous infusion, and warn against the use of intravenous bolus oxytocin, for fears of maternal haemodynamic consequences. Yet this safety concern was not based on rigorous scientific evidence but mainly derived from isolated cases and contexts that are not applicable to the majority of women undergoing low-risk vaginal birth (Hendricks 1970; Langesaeter 2009; Pinder 2002; Secher 1978; Spence 2002; Thomas 2007; Weis 1975). Davies and colleagues demonstrated that a bolus oxytocin intravenous injection of 10 IU was more effective than a dilute oxytocin infusion and not associated with adverse haemodynamic responses when used for PPH-prophylaxis in women undergoing vaginal birth (Davies 2005). On this basis, giving intramuscular oxytocin to women with established intravenous access during vaginal birth for PPH prevention may be violating the principles of best clinical practice.

Apart from the safety issues, the preference for intramuscular oxytocin might have been encouraged by its implication on the scale-up of programmes for active management of the third stage of labour. Oxytocin administration through the pre-filled Uniject device by lay health workers in primary health care and home birth settings was promoted worldwide to scale up oxytocin use in places where skilled professionals are few or non-existent (Strand 2005; Tsu 2003). This device ensures accurate dosage and safe injection practices and has been shown to be generally acceptable to both providers and mothers (Tsu 2003; Tsu 2009). In contrast, intravenous injection is less convenient for the provider, requires relatively more skill and resources, and thus cannot always be given by inexperienced providers (Van Loon 2020).

In this era of evidence-based practice and women-centred care, there are increasing efforts to move the recommended interventions for uncomplicated third stage of labour away from considerations of only effectiveness and also to include associated risks and adverse effects. As the issue of informed consent regarding routine interventions for the third stage of labour begins to gain ground (Begley 2019), practitioners would require concrete evidence on the trade-off between effectiveness and adverse effects of the two routes of oxytocin administration for mothers to make an informed choice. It is therefore important to assess whether the subtle differences in the pharmacokinetics of these routes have any implications on maternal and infant outcomes. In view of the potential implications of such clarifications on programmatic efforts to scale up the use of an effective uterotonic during the third stage of labour, it is imperative to systematically review evidence regarding the optimal route of administration of oxytocin in women undergoing vaginal birth.

This is an update of a review first published in 2012 (Oladapo 2012) and last updated in 2018 (Oladapo 2018).

OBJECTIVES

To determine the comparative effectiveness and safety of oxytocin administered intravenously or intramuscularly for prophylactic management of the third stage of labour after vaginal birth.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) or cluster-randomised trials comparing intravenous with intramuscular oxytocin administered during the third stage of labour for the prevention of PPH after a vaginal birth. We excluded quasi-randomised trials and cross-over trial designs. Potentially eligible studies, presented only as abstracts, were classified as 'Studies awaiting classification'.

Types of participants

Pregnant women anticipating a vaginal birth, regardless of other aspects of third stage of labour management.

Types of interventions

Intravenous versus intramuscular oxytocin (used alone or as part of active management of the third stage of labour) given as prophylaxis for the third stage of labour, at whatever dose, timing of administration and in whatever form (e.g. intravenous rapid or slow bolus injection or infusion). This update, as did the first review, focused only on oxytocin given during vaginal birth. Comparison of bolus oxytocin with infusion during caesarean delivery will be the subject of another review.

Types of outcome measures

We included studies whether or not they reported the following outcome measures of interest.

Primary outcomes

1. Severe PPH (blood loss of 1000 mL or more)
2. Serious maternal morbidity (organ failure, coma, intensive care unit (ICU) admission, hysterectomy, or as defined by the study authors)

Secondary outcomes

Maternal outcomes

1. Maternal death
2. PPH ≥ 500 mL
3. Estimated blood loss (mL)
4. Use of additional uterotonics
5. Blood transfusion
6. Third stage duration longer than 30 minutes
7. Retained placenta or manual removal of placenta
8. Maternal postpartum anaemia (Hb concentration less than 9 g/dL 24 to 48 hours postpartum, or as defined by study authors)

Adverse effects

1. Any adverse effect reported
2. Minor adverse effects (e.g. headache, nausea or vomiting) between birth of the baby and discharge from the labour ward
3. Major adverse effects (e.g. maternal hypotension as defined by study authors, any adverse effect requiring treatment)

Acceptability of intervention

1. Maternal dissatisfaction with intervention
2. Providers' dissatisfaction with intervention

Infant outcomes

1. Apgar score less than seven at five minutes
2. Neonatal jaundice (as defined by the study authors)
3. Admission to special care baby unit (SCBU)
4. Not breastfeeding at hospital discharge

Search methods for identification of studies

The following methods section of this review are based on a standard template used by Cochrane Pregnancy and Childbirth.

Electronic searches

For this update, we searched Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (19 December 2019).

The Register is a database containing over 25,000 reports of controlled trials in the field of pregnancy and childbirth. It represents over 30 years of searching. For methods used to populate Pregnancy and Childbirth's Trials Register, including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to Cochrane Pregnancy and Childbirth's complete and current search methods.

Briefly, Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences; and
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Two people screen the search results and review the full texts of all relevant trial reports identified through the searching activities described above. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that has been fully accounted for in the relevant review sections (Included studies; Excluded studies; Studies awaiting classification; Ongoing studies).

In addition, we searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) (19 December

2019) for unpublished, planned and ongoing trial reports (See Appendix 1 for detailed search methods).

Data collection and analysis

For methods used in the previous version of this review, see Oladapo 2018.

For this update, we used the methods described below.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted the third review author.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted the third review author. We entered data into Review Manager 5 (RevMan 5) software (RevMan 2014) and checked them for accuracy.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). Any disagreement was resolved by discussion or by involving a third review author.

(1) Random sequence generation (checking for possible selection bias)

We described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

For each included study we assessed the method as being at:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

For each included study we described the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as being at:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

For each included study we described the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding was unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as being at:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

For each included study we described the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as being at:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

For each included study, and for each outcome or class of outcomes, we described the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the study authors, we planned to re-include missing data in the analyses that we undertook.

We assessed methods as being at:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

For each included study we described how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as being at:

- low risk of bias (where it was clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's prespecified outcomes were reported; one or more reported primary outcomes

were not prespecified; outcomes of interest were reported incompletely and so could not be used; study failed to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

For each included study we described any important concerns we had about other possible sources of bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook* (Higgins 2019). With reference to (1) to (6) above, we planned to assess the likely magnitude and direction of the bias and whether we considered it was likely to have an impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses (Sensitivity analysis).

'Summary of findings' table and assessment of evidence certainty using the GRADE approach

For this update, we used the GRADE approach (Schünemann 2013) to assess the certainty of the body of evidence relating to the following outcomes for the main comparisons (intravenous versus intramuscular oxytocin in the third stage of labour).

1. Severe PPH (blood loss 1000 mL or more)
2. Serious maternal morbidity (organ failure, coma, ICU admission, hysterectomy, or as defined by the study authors)
3. Maternal death
4. PPH ≥ 500 mL
5. Use of additional uterotonics
6. Blood transfusion
7. Hypotension

We used the GRADEpro Guideline Development Tool (GRADEpro GDT 2015) to import data from RevMan 5 (RevMan 2014) in order to create a 'Summary of findings' table. We produced a summary of the intervention effect and a measure of certainty for each of the above outcomes using the GRADE approach (Schünemann 2013). The GRADE approach uses five considerations (risk of bias, consistency of effect, imprecision, indirectness and publication bias) to assess the quality (certainty) of the body of evidence for each outcome. Depending on assessment of these domains, the certainty of RCT evidence for a given outcome can be downgraded from an initial position of 'high' to 'moderate,' 'low' or 'very low.' Certainty of evidence for a given outcome may be downgraded by one level for serious limitations, or by two levels for very serious limitations (Schünemann 2013).

Measures of treatment effect

Dichotomous data

For dichotomous data, we have presented results as summary risk ratio (RR) with 95% confidence intervals (CIs).

Continuous data

We used the mean difference (MD) if outcomes were measured in the same way between studies. We planned to use the standardised mean difference (SMD) to combine studies that measured the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomised trials

We planned to include cluster-randomised trials in the analyses along with individually randomised trials; no such trials were identified for this version of the review. If we identify cluster-randomised trials for inclusion in future updates, we will adjust their sample sizes using the methods described in the *Cochrane Handbook* (Deeks 2017). Following that guidance, we will use an estimate of the intracluster correlation coefficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely (Deeks 2017).

We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Cross-over trials

Cross-over trials are not a suitable design for these interventions and are not eligible for inclusion.

Other unit of analysis issues

One of the included studies (Oguz 2014) had four study arms (two intravenous and two intramuscular groups with oxytocin administered at different times), and another two of the included studies (Charles 2019; Neri-Mejia 2016) had three arms (two intravenous groups and one intramuscular); we combined the data from the relevant arms to form a single pairwise intravenous versus intramuscular comparison.

Dealing with missing data

We noted levels of attrition in the included studies. In future updates, if more eligible studies are included, we will carry out sensitivity analyses to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effects.

As far as possible, we carried out analyses for all outcomes on an intention-to-treat basis, that is, we attempted to include all participants randomised to each group in the analyses. The denominator for each outcome in each study was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau^2, I^2 (Higgins 2003) and Chi^2 statistics (Deeks 2017). We regarded heterogeneity as substantial if I^2 was greater than 30% and either Tau^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity. If we identified

substantial heterogeneity (above 30%), we planned to explore it by prespecified subgroup analysis.

Assessment of reporting biases

In future updates, if there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it (Sterne 2017).

Data synthesis

We performed pairwise meta-analyses using a random-effects model in Review Manager software (RevMan 2014), for every comparison with at least two studies.

Subgroup analysis and investigation of heterogeneity

We investigated heterogeneity by subgroup analyses (Deeks 2017). We carried out the following subgroup analyses, for the primary outcomes of the review.

1. Intravenous oxytocin bolus injection versus infusion
2. Oxytocin used alone versus oxytocin used as part of active management of the third stage of labour (AMTSL)

In future updates, if sufficient data are available, we also plan to carry out the following subgroup analysis.

1. Oxytocin versus no oxytocin during the first stage of labour

In this update we assessed subgroup differences by interaction tests available in RevMan 5 (RevMan 2014), and reported the results quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We conducted a sensitivity analysis to explore the effect of bias risk for each comparison, by restricting analysis to those studies rated as 'low risk of bias' for random sequence generation and allocation concealment. These analyses were limited to the primary outcomes.

RESULTS

Description of studies

Results of the search

The search strategy retrieved seven new study reports for consideration in this updated review. We also reassessed three reports that were awaiting classification, and seven that were ongoing in the previous version of the review (see Figure 1).

Figure 1. Study flow diagram

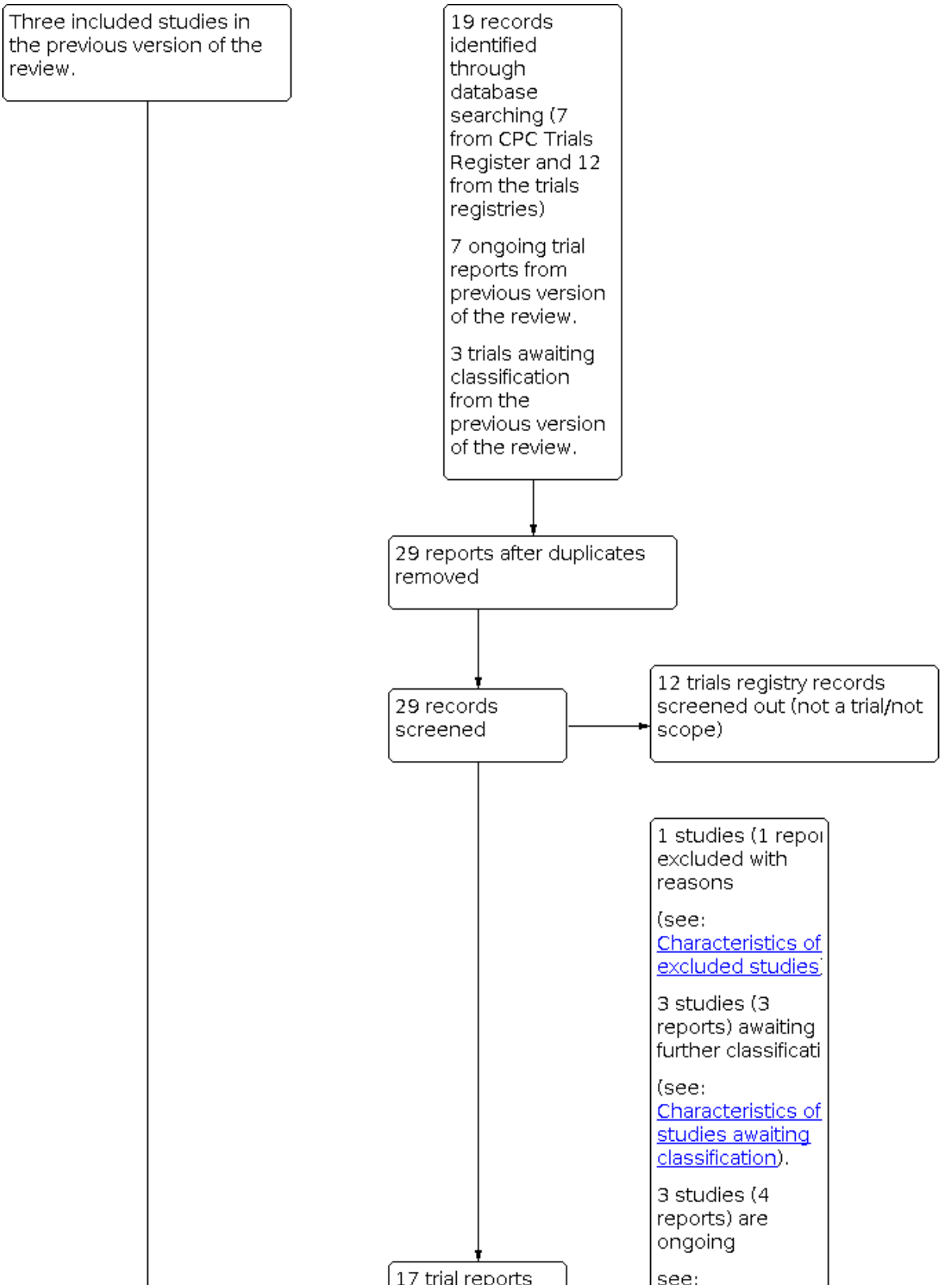
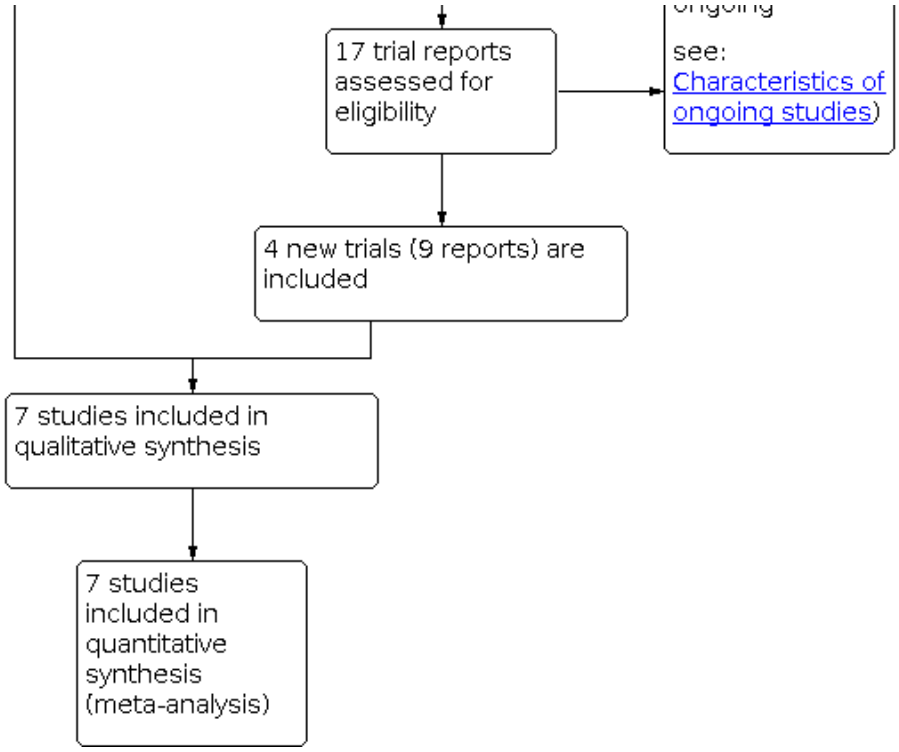


Figure 1. (Continued)



The 17 reports that we assessed corresponded to a total of 11 studies (two studies had two reports each, and another two studies had three reports each). From these 11 studies, we included four in the review (nine reports), excluded one, listed three as ongoing (four reports), and the remaining three are awaiting further assessment, pending more information from study authors or publication of the study reports (see Figure 1). For more information see Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Included studies

Design and setting

We included seven studies in this update. Included studies were conducted between 2010 and 2017. We identified one four-arm trial, two three-arm trials, and four two-arm trials. The single four-arm trial (Oguz 2014) compared intravenous bolus with intramuscular oxytocin at cord clamp and at delivery of the anterior shoulder. For the purpose of this review we combined results from the two distinct time points and treated this study as a two-arm trial. One of the three-arm trials (Charles 2019) compared oxytocin given as an intravenous bolus and oxytocin administered by an intravenous infusion with oxytocin given intramuscularly. The two intravenous arms were combined to form a single pairwise comparison in the main analysis. The other three-arm trial (Neri-Mejia 2016) compared oxytocin given as an intravenous bolus at delivery of the anterior shoulder and oxytocin intravenous infusion commencing after placental delivery with intramuscular oxytocin given at delivery of the anterior shoulder. The oxytocin infusion arm (23 women) was excluded as it occurred outside of the third stage of labour, leaving another single pairwise comparison. From the rest four two-arm trials remaining, two were double blind placebo-controlled trials (Adnan 2018; Durocher 2019), one was an open label trial (Dagdeviren 2016), and one did not provide any additional information on its design (Sangkhomkhamhang 2015).

All included studies were conducted in hospitals across six countries. One was conducted in a lower middle-income country (Egypt: Charles 2019), five were conducted in an upper middle-income countries (Argentina: Durocher 2019; Mexico: Neri-Mejia 2016; Thailand: Sangkhomkhamhang 2015; Turkey: Dagdeviren 2016, Oguz 2014), and one was conducted in a high-income country (Ireland: Adnan 2018).

Dates, sources of funding and conflict of interest of trial authors

Dates of recruitment in the studies were reported as follows: from January 2016 to December 2017 (Adnan 2018); from April 2014 to September 2015 (Charles 2019); from February 2014 to March 2015 (Dagdeviren 2016); from December 2016 to September 2017 (Durocher 2019); from August to December 2015 (Neri-Mejia 2016); from January to October 2010 (Oguz 2014); and from February to June 2012 (Sangkhomkhamhang 2015).

Funding sources were clearly reported in three studies: Trinity College, University of Dublin, and Coombe Women and Infants University Hospital (Adnan 2018); and The Bill & Melinda Gates Foundation (Charles 2019; Durocher 2019). Funding sources were not clear or not reported in the other four studies: (Dagdeviren 2016; Neri-Mejia 2016; Oguz 2014; Sangkhomkhamhang 2015)

The trial authors declared no conflicts of interest in five studies (Adnan 2018; Charles 2019; Dagdeviren 2016; Durocher 2019; Oguz 2014). Conflicts of interest were not reported in two studies (Neri-Mejia 2016; Sangkhomkhamhang 2015).

Participants

All included studies recruited women with singleton pregnancies, undergoing a vaginal birth, to whom oxytocin was administered for the third stage of labour. Most studies included term pregnancies (Adnan 2018; Dagdeviren 2016; Neri-Mejia 2016; Oguz 2014). However, even in trials without a prespecified cut off of gestational age, the vast majority of women delivered at term (Charles 2019; Durocher 2019; Sangkhomkhamhang 2015). Women with medical or obstetric complications or complications in a previous pregnancy were excluded in four of the included studies (Adnan 2018; Dagdeviren 2016; Oguz 2014; Sangkhomkhamhang 2015). In one study, the exclusion criteria were not clearly specified (Neri-Mejia 2016). In the remaining two studies, only women who had a caesarean section and those who did not provide written informed consent were excluded (Charles 2019; Durocher 2019); in one of these two studies, women who received oxytocin for induction or augmentation of labour were also excluded (Charles 2019).

Interventions

Adnan 2018 compared women receiving intravenous oxytocin 10 IU by a bolus injection with women given intramuscular oxytocin 10 IU after the birth of the baby. The cord was clamped and cut within one to three minutes after birth, except from emergency cases, and the placenta was delivered by controlled cord traction once signs of separation were apparent. Additional uterotonics were administered to women whose uteri were not adequately contracted.

Charles 2019 included three arms (two intravenous groups and one intramuscular group). In one of the intravenous arms, women received 10 IU oxytocin in 500 mL saline through a gravity-driven infusion with the roller clamp fully open. In the second intravenous arm, women received intravenous oxytocin 10 IU by a bolus injection. In the intramuscular arm, women received 10 IU oxytocin. In all three arms, oxytocin was administered after the birth of the baby. We combined the two intravenous groups to form a single intravenous group and compared this group with the intramuscular arm. Control cord traction was applied in nearly all cases and the uterus was massaged. Additional uterotonics according to local policies were administered to women whose uterus was not adequately contracted.

Dagdeviren 2016 compared women receiving intravenous oxytocin 10 IU in 1000 mL saline at 1 mL/minute with women receiving intramuscular oxytocin 10 IU after delivery of the anterior shoulder. The placenta was removed manually if not delivered within 30 minutes. The uterus was massaged and additional uterotonics were administered in cases of excessive bleeding.

Durocher 2019 compared women receiving 10 IU of intravenous oxytocin in 500 mL saline at a rate of 12 mL/minute with women who were given 10 IU of intramuscular oxytocin immediately after delivery of the baby. Control cord traction was applied in nearly all cases, and additional interventions, according to local policies, were administered to women experiencing PPH.

Neri-Mejia 2016 included three arms (two intravenous groups and one intramuscular group) two of which provided data for the purposes of this review (one of intravenous arms and the intramuscular arm). In the intravenous arm, women received 10 IU oxytocin by a bolus injection over one minute at the point of delivery of the anterior shoulder. In the intramuscular arm, women received 10 IU oxytocin at the point of delivery of the anterior shoulder. Delayed cord clamping was applied in all cases, except those where immediate resuscitation was required. The placenta was delivered by control cord traction, once signs of separation were apparent, and the uterus was massaged.

Oguz 2014 included four arms (two intravenous groups and two intramuscular groups). In the intravenous arms, both groups received 10 IU oxytocin at 1 mL/minute, with administration in one group after delivery of the baby and cord clamping, and in the other at the point of delivery of the anterior shoulder. Similarly, in the intramuscular arms, both groups of women received 10 IU oxytocin. In one group oxytocin was administered after the birth of the baby and cord clamping, while in the other, oxytocin was given at the point of delivery of the anterior shoulder. We combined the two intravenous and intramuscular arms to form a single pair-wise comparison of intravenous versus intramuscular oxytocin administration. In this study cord clamping was at one minute unless early intervention for the infant was needed.

Sangkhomkhamhang 2015 compared women who were given intravenous 10 IU of oxytocin bolus administered over two minutes with women given 10 IU of oxytocin intramuscularly. In both groups, oxytocin was administered at the point of delivery of the anterior shoulder. The placenta was removed manually if not delivered within 30 minutes. The uterus was massaged and additional uterotonics were administered in cases of excessive bleeding.

Excluded studies

We excluded two studies. One study (NCT03651882) was excluded because oxytocin was compared with carbetocin. The other study (Sheldon 2011) was a secondary analysis of data from a randomised trial comparing misoprostol plus conventional uterotonics with conventional uterotonics alone for the treatment of PPH. This secondary analysis reported results on PPH rates amongst women who had received either intravenous or intramuscular oxytocin prophylaxis during the third stage of labour. However, women included in the primary trial were randomised only after PPH diagnosis, and therefore the population was not eligible (See Characteristics of excluded studies).

Risk of bias in included studies

See Figure 2 and Figure 3 for a summary of our 'Risk of bias' assessments.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

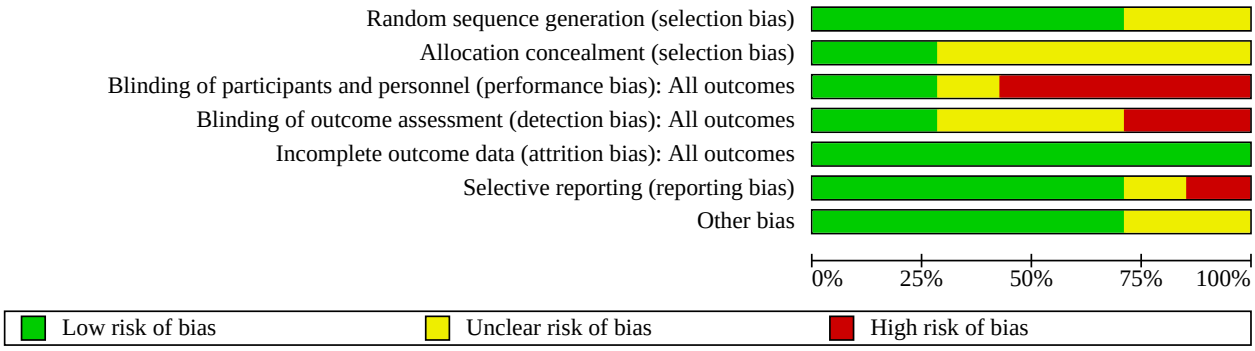
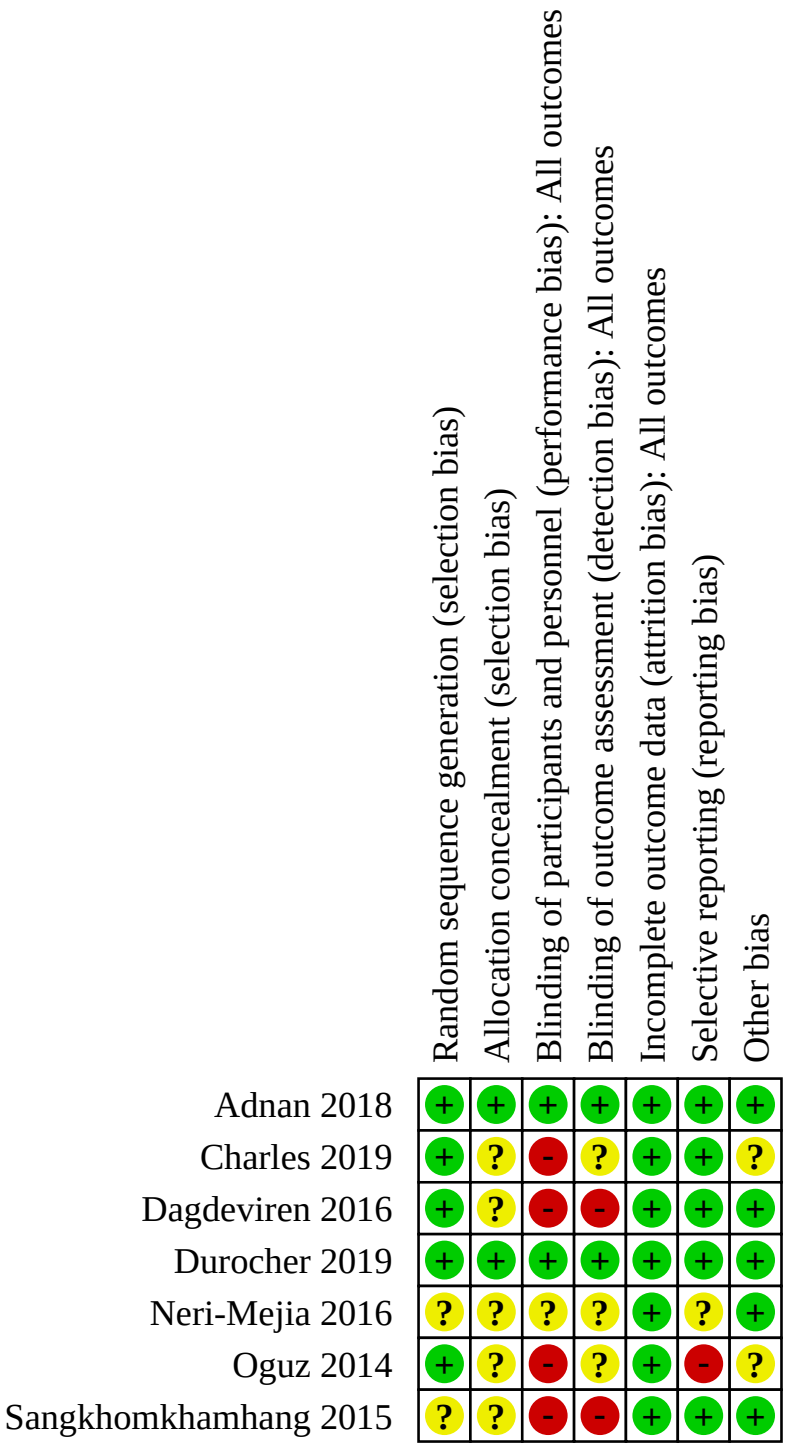


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

We judged five of the included studies (Adnan 2018; Charles 2019; Dagdeviren 2016; Durocher 2019; Oguz 2014) to be at low risk of bias for random sequence generation. Two studies (Neri-Mejia 2016; Sangkhomkhamhang 2015) did not describe their method for generating the randomisation sequence, and we judged them to be at unclear risk of bias for this domain.

Only two of the included studies (Adnan 2018; Durocher 2019) described clearly the methods of allocation concealment. We assessed them to be at low risk of bias for this domain. Four of the included trials (Dagdeviren 2016; Neri-Mejia 2016; Oguz 2014; Sangkhomkhamhang 2015) did not clearly describe how allocation concealment was achieved at the point of randomisation, and we judged them to have an unclear risk of bias for this domain. One trial (Charles 2019) used sealed opaque envelopes to conceal the allocation. However, random sequence was generated in blocks of seven. We judged this study to be at unclear risk for allocation concealment, given that personnel might have been able to break the randomisation code.

Blinding

In two of the included studies (Adnan 2018; Durocher 2019) participants and personnel were masked to treatment allocation, and we assessed these studies to be at low risk of bias for this domain. In contrast, participants and personnel in four of the included studies (Charles 2019; Dagdeviren 2016; Oguz 2014; Sangkhomkhamhang 2015) were aware of treatment allocation, and therefore we assessed these studies to be at high risk of performance bias. Neri-Mejia 2016 is stated to be a blinded study but no additional information was made available.We judged this study to be at unclear risk of performance bias.

Only two of the included studies (Adnan 2018; Durocher 2019) described adequate methods for blinding outcome assessors, and thus we judged them to be at low risk of detection bias. Another two studies (Dagdeviren 2016; Sangkhomkhamhang 2015) did not blind outcome assessors to treatment allocation, and we assessed them to be at high risk of bias for this domain, as lack of blinding may have had an impact on subjective outcomes. Neri-Mejia 2016 is stated to be a blinded study but no additional information was made available. Charles 2019 and Oguz 2014 reported that staff assessing blood loss outcomes were blinded to group allocation, but it was not clear whether or not blinding was effective for the remaining outcomes. We assessed these three studies to be at an unclear risk of detection bias.

Incomplete outcome data

In the study by Adnan 2018, we noted that > 10% data on postpartum haemoglobin levels were missing across both study arms. Therefore, we assessed it to be at high risk of bias for Hb related outcomes but low risk overall. We assessed all other studies to be at low risk of attrition bias.

Selective reporting

Four of the included studies (Adnan 2018; Charles 2019; Dagdeviren 2016; Durocher 2019) were prospectively registered, and fully reported all prespecified outcomes. We judged these studies to be at low risk of reporting bias. We were unable to identify a registered protocol for Neri-Mejia 2016, and therefore we judged this study to be at an unclear risk of reporting bias. Oguz 2014 was registered retrospectively and did not report some important outcomes. In addition, while the background sections of the paper mentioned blood loss greater than 500 mL (the usual cut-off for PPH), the outcome reported in this study was blood loss greater than 600 mL. While Sangkhomkhamhang 2015 was registered and did collect data on expected outcomes, they did not fully report all outcomes. Nevertheless, we assessed this study to be at low risk of bias for this domain.

Other potential sources of bias

Other sources of bias were not apparent in most of the included studies (Adnan 2018; Dagdeviren 2016; Durocher 2019; Neri-Mejia 2016; Sangkhomkhamhang 2015). Two of the included studies had a baseline difference between groups. In Charles 2019 one group had higher episiotomy rates, whereas in Oguz 2014 one group had a greater proportion of women undergoing induction of labour. Since these differences may have had an impact on outcomes of interest, we assessed these studies to be at unclear risk of other bias. Three studies were funded by university and hospital grants (Adnan 2018) or received financial support from foundations (Charles 2019; Durocher 2019). The remaining four studies did not provide information on the source of funding. In most of the included studies, authors declared no conflicts of interest. However, in two cases (Neri-Mejia 2016; Sangkhomkhamhang 2015) conflicts of interest were not reported.

Effects of interventions

See: **Summary of findings 1** Intravenous compared to intramuscular oxytocin for PPH prevention

Primary outcomes

Severe PPH (blood loss of 1000 mL or more)

Four trials, involving 6681 women, reported data for severe PPH. Based on relative effects from pairwise meta-analysis, intravenous (bolus or infusion) oxytocin compared with intramuscular oxytocin probably reduces blood loss of 1000 mL or more, although the 95% confidence interval (CI) crosses the line of no-effect (average RR 0.65, 95% CI 0.39 to 1.08; moderate-certainty evidence; Summary of findings 1). Three of the available studies reported a higher event rate in the intramuscular arm, whereas one small study (256 women) presented contradictory results. The latter contributed only 2.9% weight to the pooled effect estimate, but had a serious effect on the observed heterogeneity (I^2 = 30%). By excluding this small study, the CI no longer crossed the line of no-effect and the treatment effect favoured intravenous oxytocin (RR 0.61, 95% CI 0.42 to 0.88; high-certainty evidence; analysis not shown).

Subgroup analysis based on the mode of administration of intravenous oxytocin (bolus injection or infusion) versus intramuscular oxytocin did not show any substantial differences (Chi^2 = 0.46, (P = 0.50); I^2 = 0% for subgroup differences, Analysis 2.1). Similarly, subgroup analysis based on whether oxytocin was used alone or as part of active management of the third stage of labour (AMTSL) did not show any substantial differences between the two routes of administration (Chi^2 = 3.25, (P = 0.07); I^2 = 69.2% for subgroup differences, Analysis 3.1). We could not perform one of the planned subgroup analyses, oxytocin versus no oxytocin during the first stage of labour, as it was not clear in the included trials whether or not women had oxytocin augmentation (see Methods).

Sensitivity analysis exploring the effect of bias risk, by restricting analysis to those studies rated as 'low risk of bias' for random sequence generation and allocation concealment, found that intravenous administration of oxytocin reduces the risk for PPH ≥ 1000 mL compared with intramuscular administration of oxytocin (average RR 0.64, 95% CI 0.43 to 0.94; Analysis 4.1).

Serious maternal morbidity (organ failure, coma, ICU admission, hysterectomy, or as defined by the study authors)

Four trials, involving 7028 women, reported results for serious maternal morbidity. Although intravenous compared with intramuscular administration of oxytocin probably results in a lower risk for serious maternal morbidity (organ failure, coma, ICU admissions, hysterectomy), the CI suggests a substantial reduction to no reduction in the risk for serious maternal morbidity (average RR 0.47, 95% CI 0.22 to 1.00; moderate-certainty evidence; Summary of findings 1). A single study reported the most events (97%) which corresponded to women admitted to the high dependency unit (HDU). In contrast, remaining studies reported zero events, apart from one case of uvular oedema. It is very much likely that these women were admitted to the HDU only for observation, given that the study reported no hysterectomies or ICU admissions, and was conducted in a high-income country with multiple available resources.

The subgroup effects by type of intravenous oxytocin administration (bolus or infusion) remained unclear, as all trials comparing oxytocin given as an intravenous infusion with oxytocin given intramuscularly reported zero events (Analysis 2.2). Subgroup analysis by whether oxytocin was used with or without AMTSL did not show any substantial differences between the two routes of administration (Chi^2 = 0.04, df = 1 (P = 0.83); I^2 = 0%, Analysis 3.2). We could not perform one of the planned subgroup analyses (oxytocin versus no oxytocin during the first stage of labour) as it was not clear in the included trials whether or not women had oxytocin augmentation (see Methods).

Sensitivity analysis exploring the effect of bias risk, by restricting analysis to those studies rated as 'low risk of bias' for random sequence generation and allocation concealment, found that prophylactic intravenous administration of oxytocin probably reduces the risk for serious maternal morbidity compared with intramuscular oxytocin (average RR 0.47, 95% CI 0.22 to 1.04; Analysis 4.2). However, the 95% CI crosses the line of no-effect.

Secondary outcomes

Maternal death

Four of the included studies (involving 7028 women) reported maternal death as an outcome. However, there were no maternal deaths in any of these studies. Therefore, it is unclear whether the route of oxytocin administration has any effect on maternal mortality related to PPH (Summary of findings 1).

PPH (blood loss of 500 mL or more)

Six trials (involving 7731 women) contributed data for PPH of 500 mL or more. Intravenous administration of prophylactic oxytocin reduces the risk for PPH ≥ 500 mL compared with intramuscular administration of oxytocin (average RR 0.78, 95% CI 0.66 to 0.92; high-certainty evidence; Summary of findings 1).

Mean blood loss

Six trials (involving 7518 women) provided data for mean blood loss. Although the data have been presented as reported in these trials, the data were not pooled because the reported standard deviations (SDs) varied considerably. While these studies generally suggest that blood loss may have been slightly reduced in the intravenous group compared with the intramuscular group, the mean loss was low and the minor differences between groups are unlikely to be clinically important (Analysis 1.5).

Use of additional uterotonics

Six trials (involving 7327 women) reported results regarding the use of additional uterotonics. Intravenous administration of oxytocin may make little or no difference to the use of additional uterotonics compared with intramuscular administration of oxytocin (average RR 0.78, 95% CI 0.49 to 1.25; low-certainty evidence; Summary of findings 1).

Blood transfusion

Four trials (involving 6684 women) reported blood transfusion as an outcome. Intravenous administration of oxytocin reduces the need for blood transfusion compared with intramuscular administration of oxytocin (average RR 0.44, 95% CI 0.26 to 0.77; high-certainty evidence; Summary of findings 1).

Third stage duration longer than 30 minutes

Only one trial with 450 women provided data for prolonged third stage of labour. It is unclear whether intravenous administration of oxytocin shortens the third stage of labour compared with intramuscular administration of oxytocin because the certainty of this evidence is very low (Analysis 1.8).

Mean duration of third stage (minutes)

We did not pre-specify this outcome.

Three trials (involving 1121 women) reported mean duration of third stage of labour. Although we have displayed the data as reported, we decided not to pool the results as the means and reported SDs in the three studies varied considerably (Analysis 1.9).

Retained placenta or manual removal of the placenta

Five trials (involving 6292 women) reported results regarding the incidence of retained placenta or manual removal of the placenta. Intravenous administration of oxytocin may reduce the incidence of retained placenta or manual removal of the placenta compared with intramuscular administration of oxytocin, although the 95% CI crosses the line of no-effect (average RR 0.73, 95% CI 0.52 to 1.03; low-certainty evidence; Analysis 1.10). Most weight (92.5%) of the pooled effect estimate was provided by a single study of moderate quality.

Maternal postpartum anaemia

Three of the included trials (involving 6188 women) contributed data for maternal postpartum anaemia. Intravenous administration of oxytocin probably makes little or no difference to this outcome when compared with intramuscular administration of oxytocin (average RR 0.99, 95% CI 0.84 to 1.16; moderate-certainty evidence; Analysis 1.11).

Mean postpartum haemoglobin levels (g/L)

We did not pre-specify this outcome.

Two trials (involving 856 women) contributed data for mean postpartum haemoglobin levels. However, the generated evidence from pairwise meta-analysis was of very low certainty, and the relative effects of intravenous and intramuscular oxytocin remained unclear (Analysis 1.12).

Any adverse effect reported

One trial (involving 1035 women) contributed data for any side effect. Based on results from this single study, intravenous administration of oxytocin compared with intramuscular administration of oxytocin probably makes little or no difference to this outcome (average RR 0.78, 95% CI 0.45 to 1.36; moderate-certainty evidence; Analysis 1.13).

Nausea

Two trials (involving 1515 women), contributed data for nausea. However, only one trial (1035 women) reported events and provided the whole weight of the pooled effect estimate. Intravenous administration of oxytocin may not increase the incidence of nausea when compared to intramuscular administration of oxytocin (average RR 1.00, 95% CI 0.06 to 15.98; low-certainty evidence; Analysis 1.14).

Vomiting

Two of the included trials (involving 1515 women) reported vomiting as an outcome. However, there were no cases of vomiting in any of these studies. Therefore, it is unclear whether the route of oxytocin administration has any effect on the occurrence of vomiting (Analysis 1.15).

Diarrhoea

One trial with 480 women reported diarrhoea as an outcome. However, there were no events of diarrhoea in this study. Therefore, it is unclear whether the route of oxytocin administration has any effect on the occurrence of diarrhoea (Analysis 1.16).

Fever (> 38ºC)

One trial with 480 women reported fever as an outcome. However, there were no events of fever in this study. Therefore, it is unclear whether the route of oxytocin administration has any effect on the occurrence of fever > 38ºC (Analysis 1.17).

Shivering

Two trials (involving 1515 women), reported shivering as an outcome. However, only one trial (1035 women) reported events and provided the whole weight of the pooled effect estimate. Intravenous administration of oxytocin compared with intramuscular administration of oxytocin may not increase the risk for shivering (average RR 0.40, 95% CI 0.08 to 2.06; low-certainty evidence; Analysis 1.18).

Headache

Two trials (involving 1515 women) reported data on the incidence of headache. However, only one trial (1035 women) reported events and provided the whole weight of the pooled effect estimate. Intravenous administration of oxytocin may not increase the incidence of headache when compared with intramuscular administration of oxytocin (average RR 0.75, 95% CI 0.17 to 3.34; low-certainty evidence; Analysis 1.19).

Hypotension

Four trials (involving 6468 women) provided data for hypotension. Intravenous administration of oxytocin probably makes little or no difference to the risk of hypotension compared with intramuscular administration of oxytocin (average RR 1.01, 95% CI 0.88 to 1.15; moderate-certainty evidence; Summary of findings 1).

Tachycardia

Two trials (involving 1513 women) contributed data for tachycardia. Intravenous administration of oxytocin probably makes little or no difference to tachycardia when compared with intramuscular administration of oxytocin (average RR 0.89, 95% CI 0.68 to 1.16; moderate-certainty evidence; Analysis 1.21).

Acceptablilty of the intervention

None of the included studies reported either women's or provider's satisfaction with routes of oxytocin administration.

Infant outcomes

Apgar score less than seven at five minutes, neonatal jaundice, and SCBU admission were not reported by any of the included studies

One study (involving 1035 women) reported data on infants not breastfeeding at hospital discharge. Intravenous administration of oxytocin has little or no effect on number of infants not breastfeeding at hospital discharge when compared with intramuscular administration of oxytocin (average RR 0.96, 95% CI 0.84 to 1.10; high-certainty evidence; Analysis 1.27).

DISCUSSION

Summary of main results

There is high-certainty evidence to suggest that intravenous administration of oxytocin compared with its intramuscular administration reduces the risk for PPH ≥ 500 mL and blood transfusion following vaginal birth. Although oxytocin given intravenously probably reduces the risk of severe PPH ≥ 1000 mL, the confidence interval crosses the line of no-effect and thus it is also compatible with no reduction. However, if we remove one small study whose findings contradicted the results of the remaining available trials, then oxytocin given intravenously reduces the risk for PPH ≥ 1000 mL. Additionally, in a sensitivity analysis exploring the effect of bias risk, we found that intravenous administration of oxytocin reduces the risk of severe PPH compared with intramuscular administration among studies at low risk of bias. The two routes of oxytocin administration may be comparable in terms of additional uterotonic use. While there are probably fewer cases of serious maternal morbidity amongst women given oxytocin intravenously compared with those receiving oxytocin intramuscularly, the confidence interval ranging from a substantial risk reduction to no-effect are not reassuring. In this case the pooled effect estimate was mostly provided by a single study from a high-income country (Ireland) reporting on HDU admissions. The remaining three trials reported zero events of serious maternal morbidity with the exception of one case of uvular oedema. There were no maternal deaths reported in any of the included

studies. Overall, the side effects profiles of the two routes of oxytocin administration, including incidence of hypotension, are comparable.

Subgroup analyses based on the mode of administration of intravenous oxytocin (bolus injection versus infusion) and whether oxytocin administration was in the context of AMTSL did not show any substantial differences on the primary outcomes.

Overall completeness and applicability of evidence

We identified seven studies conducted within the last decade mostly from middle-income and high-income settings among the population of interest for this review. All studies applied the oxytocin dose (10 IU) that is currently recommended by the WHO. The studies included the common modalities of administering intravenous oxytocin and tested comparative efficacy and safety of the two routes of oxytocin administration in the context of standard care for PPH prevention. While the findings of our review should be generalisable in terms of tested intervention and control oxytocin regimen and PPH preventive measures, it is uncertain whether the clinical benefits in favour of intravenously administered oxytocin would be demonstrated in low-income settings where several other factors could affect safety of intravenous medications.

Quality of the evidence

The studies contributing data to the review were mostly at moderate or low risk of bias. Two studies did not clearly describe methods of random sequence generation, and five were judged to be at unclear risk for allocation concealment. Most studies were judged to be at high or unclear risk of performance and detection bias. Two high-quality trials administered matching placebo and were assessed as low risk of bias for the relevant domains. All studies reported objective measurements of blood loss, and were also judged to be at low risk for attrition bias.

Using the GRADE approach for appraisal of the certainty of evidence, our confidence in the effect estimates of this review for the GRADE outcomes (PPH ≥ 1000 mL, serious maternal morbidity, maternal death, PPH ≥ 500 mL, use of additional uterotonics, blood transfusion, hypotension) ranged from very low to high, with the evidence for PPH ≥ 500 mL and blood transfusion being of high certainty. See Effects of interventions and Summary of findings 1.

Potential biases in the review process

We minimised potential bias by the use of a comprehensive search strategy. Two review authors independently assessed eligibility and certainty of evidence, and performed data extraction.

The growing interest in women-centred care has shifted evaluation of best practice beyond effectiveness alone to include adverse effects and acceptability of interventions. We examined the study reports for information on adverse events, even though the included studies provided little or no data on them.

A source of bias in this review may be the inconsistent definition of PPH in the included studies, but also differences in the specific management of third stage of labour, and the mode of intravenous oxytocin administration, i.e. either bolus injection or infusion. We have explored this clinical heterogeneity by carrying out subgroup analyses for the primary outcomes, which did not show any substantial differences. However, the sensitivity analysis restricting analysis to those studies rated as 'low risk of bias' found that intravenous administration of oxytocin reduces the risk for PPH ≥ 1000 mL compared with intramuscular oxytocin. This suggests that the study quality could have affected the overall effects observed in this review. Bias in this review was, however, reduced by the decision not to pool individual study data on 'mean blood loss' and 'mean duration of 3rd stage' where means and reported SDs varied considerably.

Agreements and disagreements with other studies or reviews

In a Cochrane Review to determine the effects of oxytocin used for the prophylactic management of the third stage of labour (Salati 2019), the review authors noted that the included studies provided insufficient data to examine the role of different routes of oxytocin administration. However, a number of new studies have been included in this update, which has changed the conclusion of our previous review (Oladapo 2018). The finding of clinical benefit in the absence of any safety concern when oxytocin is given intravenously does not support previous observations suggesting increased harms with intravenous compared with intramuscular oxytocin administration (Pinder 2002; Svanström 2008).

AUTHORS' CONCLUSIONS

Implications for practice

Intravenous administration of oxytocin appears to be more effective than its intramuscular administration in preventing postpartum hemorrhage (PPH) during vaginal birth. Intravenous oxytocin administration presents no additional safety concerns and has a comparable side effects profile with intramuscular oxytocin administration.

Health practitioners who provide care to women during labour should be aware of this evidence and be guided in their choice of the route of oxytocin administration for PPH prevention. While the balance of effects favours intravenous oxytocin administration for important health outcomes, health managers and policy-makers would need to consider the scale up of this intervention in the context of its feasibility and impact on available resources, health equity and women's comfort, as well as potential safety concerns in settings where precautionary measures cannot be guaranteed. Establishing an intravenous access early in the intrapartum period for the sole purpose of administering prophylactic oxytocin during the third stage may increase the overall use of unnecessary labour interventions, including routine use of intravenous fluids. However, in instances where women already have an intravenous access in place during a vaginal birth (for another medical indication), it is reasonable to take advantage of the additional clinical benefits that intravenous administration of oxytocin provides. Most importantly, it is crucial that women are supported in their choice of the route of oxytocin administration and be involved in decision-making.

Implications for research

Future studies on the routes of oxytocin administration for the management of the third stage of labour should give importance to study design (especially allocation concealment and blinding of outcome assessment) in order to improve the quality of the research evidence.

In this era of woman-centred maternity care, future studies could identify and report critical outcome measures that are important to women. Such studies should also consider acceptability of the intervention to mothers and providers as important outcomes, and feasibility and resource use related to intravenous administration of oxytocin.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Adnan 2018

Study characteristics

Adnan 2018 *(Continued)*

Methods	2-arm double-dummy randomised controlled trial
Participants	**Setting:** university affiliated maternity unit in the Republic of Ireland. **Dates of recruitment:** from January 2016 to December 2017. **Total randomised:** 1075 women with full cervical dilation and an urge to push if multiparous, or when delivery was imminent. **Inclusion criteria:** women aged 18 years or older with a singleton term pregnancy (≥ 37 weeks), aiming for a vaginal birth. **Exclusion criteria:** women at an increased risk of PPH, whose caregiver had pre-decided to administer an additional oxytocin infusion, including those with a history of atonic PPH, fibroids, coagulopathy and those receiving anticoagulant treatment, and those with thrombocytopenia. Women with pre-existing cardiovascular disease, and those who did not understand English were also excluded.
Interventions	**Experimental intervention**: IV oxytocin 10 IU in 1 mL over 1 minute and 1 mL 0.9% normal saline as placebo intramuscularly immediately after the delivery of the baby. Total number randomised = 517 women. **Control/comparison intervention**: IM oxytocin 10 IU in 1 mL and 1 mL 0.9% normal saline as placebo intravenously over 1 minute immediately after the delivery of the baby. Total number randomised = 518 women. The cord was clamped and cut within 1-3 minutes after birth, except from emergency cases. The placenta was delivered by controlled cord traction once signs of separation were apparent. Additional uterotonics according to local policies were administered to women whose uterus was not adequately contracted. Women were observed for at least 1 hour after birth.
Outcomes	Severe PPH ≥ 1000 mL, serious maternal morbidity, maternal death, PPH ≥ 500 mL, mean blood loss, use of additional uterotonics, need for blood transfusion, manual removal of the placenta, maternal postpartum anaemia (defined as a decrease in haemoglobin levels by ≥ 20% 24 hours after delivery), any side effect, nausea, vomiting, shivering, headache, hypotension (defined as BP > 30% lower than predelivery measurements or use of ephedrine, or both), tachycardia, not breastfeeding at time of discharge.
Notes	**Funding:** Trinity College, University of Dublin, and Coombe Women and Infants University Hospital. **CoI:** the authors declared no conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reported that random sequence was computer generated with blocks of varying size.
Allocation concealment (selection bias)	Low risk	A research fellow who was not involved in patient management randomised women during the second stage of labour and prepared the trial syringes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Only the research fellow was aware of treatment allocation. Personnel involved in patient management and trial participants were both masked to treatment allocation. Matching placebo was used for trial purposes.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded to treatment allocation.

Adnan 2018 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	40 women undergoing caesarean section were excluded after randomisation. Data were routinely collected from all remaining randomised study participants (1035) and analyzed on an intention-to-treat basis. However, balanced attrition bias > 10% was noted in haemoglobin measurements.
Selective reporting (reporting bias)	Low risk	This was a prospectively registered study (ISRCTN14718882) and all prespecified outcomes were fully reported.
Other bias	Low risk	Groups appeared similar at baseline and authors describe objective methods of measuring blood loss. No apparent source of bias.

Charles 2019

Study characteristics	
Methods	3-arm open-label active-controlled randomised trial
Participants	**Setting:** 1 teaching hospital in Cairo and 1 University hospital in Alexandria, Egypt. **Dates of recruitment:** from April 2014 to September 2015. **Total randomised:** 4913 women. **Inclusion criteria:** women who had received no pre-delivery oxytocin (for induction or augmentation of labour) and had a live birth vaginally. **Exclusion criteria:** women who received oxytocin pre-delivery, those who had a caesarean section, and those who were unable to provide written informed consent.
Interventions	**Experimental intervention**: IV oxytocin 10 IU in 500 mL saline through gravity-driven infusion with the roller clamp fully open after the delivery of the baby. Total number randomised = 2108 women. **Experimental intervention**: IV oxytocin 10 IU oxytocin over 1 minute after the delivery of the baby. Total number randomised = 701 women. **Control/comparison intervention**: IM oxytocin 10 IU after the delivery of the baby. Total number randomised = 2104 women. We have combined the 2 IV groups to form a single IV versus IM comparison. Information were collected on control cord traction and uterine massage. Additional uterotonics according to local policies were administered to women whose uterus was not adequately contracted. Women were observed and postpartum blood loss was measured 1 hour after birth.
Outcomes	Severe PPH ≥ 1000 mL, serious maternal morbidity, maternal death, PPH ≥ 500 mL, mean blood loss, use of additional uterotonics, blood transfusion, mean duration of 3rd stage, manual removal of the placenta, maternal postpartum anaemia (defined as a decrease in haemoglobin levels by ≥ 2 g/dL 24 hours after delivery, excluding women who received a blood transfusion), hypotension (defined as Systolic BP ≤ 90 mmHg, or Diastolic BP ≤ 60 mmHg).
Notes	**Funding:** The Bill & Melinda Gates Foundation. **CoI:** the authors declared no conflicts of interest.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Charles 2019 *(Continued)*

Random sequence generation (selection bias)	Low risk	The random sequence was computer-generated in blocks of 7 by Gynuity Health Projects, New York.
Allocation concealment (selection bias)	Unclear risk	Sequentially sealed opaque envelopes were used to conceal the allocation. Small blocked randomisation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	According to study protocol and report, there was no attempt to mask participants and personnel to treatment allocation. Staff providing care and making clinical decisions would be aware of which intervention women received.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Effort was made to blind the outcome assessors but it is unclear if this was a successful approach. 'We minimized provider bias by having staff other than the administering provider assess blood loss using calibrated containers'.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were routinely collected from all randomised study participants and analyzed on an intention-to-treat basis.
Selective reporting (reporting bias)	Low risk	This was a prospectively registered study (NCT01914419) and all prespecified outcomes were fully reported.
Other bias	Unclear risk	Groups appeared similar at baseline except from episiotomy rates. Authors describe objective methods of measuring blood loss. No other apparent source of bias.

Dagdeviren 2016

Study characteristics	
Methods	RCT with individual randomisation
Participants	**Setting:** teaching hospital in Istanbul, Turkey. **Dates of recruitment:** from February 2014 to March 2015. **Total randomised:** 256 women at the point when delivery was “imminent”. **Inclusion criteria**: women aged 18-45 years, singleton term pregnancy (37-42 weeks), cephalic presentation, normal blood pressure (< 140/90 mmHg), intending to have vaginal birth. **Exclusion criteria**: grand multiparity (although it was not clear how this was defined as parity ranged from 1-6 in women recruited), Hb < 7 g/dL, prolonged 1st stage of labour, induction (oxytocin for ≥ 12 hours), previous caesarean birth or uterine surgery, uterine myoma or serious obstetric or other comorbidity, previous PPH, history of coagulopathies and anticoagulant treatment around the time of delivery, haemorrhage during current pregnancy, history of placental abruption, macrosomia or polyhydramnios.
Interventions	**Experimental intervention**: IV oxytocin 10 IU in 1000 mL saline at a rate of 1 mL/minute after delivery of the anterior shoulder. Total number randomised = 128 women. **Control/comparison intervention**: IM oxytocin 10 IU after delivery of the anterior shoulder. Total number randomised = 128 women. In both groups the placenta was removed manually if it was not delivered within 30 minutes. If there was excessive bleeding the uterus was massaged bimanually for at least 15 seconds and additional uterotonics (20 IU oxytocin in 1000 mL saline solution and IM methylergometrine maleate 0.2 mg) were

Dagdeviren 2016 *(Continued)*

	administered. Observations were recorded every 15 minutes in the 1st hour and every 30 minutes in the 2nd hour after birth.
Outcomes	Blood loss (measured by gauge in blood collection bag and weighing tampons and swabs (gauze used during episiotomy and perineal repair not included). Primary PPH (blood loss ≥ 500 mL) within 24 hours, blood loss ≥ 1000 mL, need for blood transfusion, additional uterotonics or manual removal of the placenta, mean duration of 3rd stage, prolonged 3rd stage (> 30 minutes), mean postpartum Hb, and side effects.
Notes	**Funding:** source of study funding not clear. **CoI:** stated that authors had no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reported that a random number table was used to determine the sequence for randomisation.
Allocation concealment (selection bias)	Unclear risk	The way women were allocated to groups at the point of randomisation was not clear. It was stated that women were divided into 2 “equal” groups and randomisation was at the point when delivery was imminent.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Staff providing care and making clinical decisions about interventions would be aware of which intervention women received; this may have had an impact on outcomes such as estimated blood loss and need for additional interventions. The study protocol stated that there was no attempt to mask treatment from women and personnel.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes would be recorded by staff aware of allocation and this may have had an impact on subjective outcomes such as estimates of blood loss. For outcomes such as postpartum Hb measured 24 hours after the birth, the impact of lack of blinding may have been low.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The study flow diagram and tables suggest there was no loss to follow-up. It was not clear if there were any missing data for particular outcomes.
Selective reporting (reporting bias)	Low risk	This was a registered study (NCT02080104) and expected outcomes were reported. Incidence of prolonged 3rd stage was not reported, but duration was reported as a mean.
Other bias	Low risk	Groups appeared similar at baseline and other bias was not apparent. It was not clear what usual practice had been in the study hospital prior to the study.

Durocher 2019

Study characteristics

Methods	2-arm double-dummy randomised controlled trial
Participants	**Setting:** tertiary-level hospital in Corrientes, Argentina.

Durocher 2019 *(Continued)*

	Dates of recruitment: from December 2016 to September 2017. **Total randomised:** 480 women at the point when delivery was "imminent". **Inclusion criteria:** women in active labour with a live fetus, undergoing vaginal delivery. **Exclusion criteria:** women who had a caesarean delivery and those who were unable to provide informed consent.
Interventions	**Experimental intervention**: IV oxytocin 10 IU in 500 mL saline solution at a rate of 12 mL/minute and 1 ampoule intramuscularly immediately after delivery of the baby. Total number randomised = 239 women. **Control/comparison intervention**: IM oxytocin 10 IU and 1 ampoule in 500 mL saline solution as placebo intravenously at a rate of 12 mL/minute immediately after the delivery of the baby. Total number randomised = 241 women. Information were collected on control cord traction. Pulse and blood pressure were measured at 15-minute intervals for 1 hour postpartum. Additional interventions, according to local policies, were administered to women experiencing PPH. Blood loss was recorded at time of PPH diagnosis and at cessation of active bleeding. Blood loss amounts were routinely recorded for all participants at 30 and 60 minutes postpartum. A second haemoglobin measurement was conducted at 24–48 hours postpartum.
Outcomes	Severe PPH ≥ 1000 mL, serious maternal morbidity, maternal death, PPH ≥ 500 mL, mean blood loss, use of additional uterotonics, blood transfusion, mean duration of 3rd stage, manual removal of the placenta, maternal postpartum anaemia (defined as a decrease in haemoglobin levels by ≥ 2 g/dL 24-48 hours after delivery), mean postpartum Hb. We retrieved through personal communication with the study authors data regarding: ICU admissions, nausea, vomiting, diarrhoea, fever, shivering, headache, hypotension, and tachycardia.
Notes	**Funding:** The Bill & Melinda Gates Foundation. **CoI:** the authors declared no conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The random sequence was computer-generated in blocks of 10 by Gynuity Health Projects, New York.
Allocation concealment (selection bias)	Low risk	Sequentially numbered study packets were used to conceal allocation. The next packet was removed from the dispenser when birth was imminent.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Care providers and participants were masked to treatment allocation. Matching placebo was used for trial purposes. The randomisation code was not shared with hospital staff or local investigators.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition bias was noted for some of the outcomes, but it was < 10% and balanced across study arms.
Selective reporting (reporting bias)	Low risk	This was a prospectively registered study (NCT02954068) and all prespecified outcomes were fully reported.

Durocher 2019 *(Continued)*

Other bias	Low risk	Groups appeared similar at baseline and authors describe objective methods of measuring blood loss. No apparent source of bias.

Neri-Mejia 2016

Study characteristics	
Methods	3-arm active-controlled randomised trial
Participants	**Setting:** regional hospital in Zaragoza, Mexico. **Dates of recruitment**: from August to December 2015. **Total randomised:** 66 women (23 excluded from the review analysis) **Inclusion criteria:** women with a singleton term pregnancy, cephalic presentation, no evident cephalopelvic disproportion, and spontaneous or induced onset of labour, undergoing vaginal delivery, who provided written informed consent, and whose haemoglobin was measured during labour. **Exclusion criteria:** not clearly specified.
Interventions	**Experimental intervention**: IV oxytocin 10 IU over 1 minute after the delivery of the anterior shoulder. Total number randomised = 21 women. **Experimental intervention**: IV oxytocin 20 IU in 1000 mL 5% glucose solution at a rate of 150 mL/hour after the delivery of the placenta. Total number randomised = 23 women. This arm was excluded for the purposes of this review, since intervention was administered after the third stage of labour. **Control/comparison intervention**: IM oxytocin 10 IU after the delivery of the anterior shoulder. Total number randomised = 22 women. Delayed cord clamping was applied in all cases, except those were immediate resuscitation was required. The placenta was delivered by control cord traction, once signs of separation were apparent, while uterus was massaged. Haemoglobin and haematocrit measurements were repeated 12 hours postpartum.
Outcomes	Mean blood loss, use of additional uterotonics, mean duration of 3rd stage, retained placenta, mean postpartum Hb, hypotension.
Notes	**Funding:** the source of funding was not reported. **CoI:** not reported, if any.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	It is stated to be a randomised trial, though the method of sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Methods of allocation concealment were not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It is stated to be a blinded study, but no additional information was reported.

Neri-Mejia 2016 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is stated to be a blinded study, but no additional information was reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Text and tables suggest that there was no loss to follow-up. However, it was not clear, whether there were any missing data for particular outcomes.
Selective reporting (reporting bias)	Unclear risk	The study protocol was unavailable for verification.
Other bias	Low risk	Groups appeared similar at baseline and authors describe objective methods of measuring blood loss. No apparent source of bias.

Oguz 2014

Study characteristics	
Methods	RCT with individual randomisation
Participants	**Setting:** teaching hospital in Ankara, Turkey. **Dates of recruitment:** from January to October 2010. **Total randomised:** 600 women. **Inclusion criteria**: singleton pregnancy with cephalic presentation > 37 weeks, in active phase of labour, with normal vaginal birth. **Exclusion criteria**: fetal death, multiple pregnancy, coagulation disorder, placental pathology, liver disease, thrombocytopenia, hypertension or taking anticoagulants, caesarean or operative birth, deep vaginal tear, chorioamnionitis, HELLP syndrome, disseminated intravascular coagulation before delivery.
Interventions	**Experimental intervention**: 2 IV groups (150 women in each). Both groups received 10 IU IV oxytocin at 1 mL/minute, in group IV (A) this was given after delivery of the baby and cord clamping, in group IV (B) oxytocin was given at the point of delivery of the anterior shoulder. Total number randomised = 300 in IV group. **Control/comparison intervention**: 2 IM groups (150 women in each). Both groups received 10 IU IM oxytocin, in group IM (A) this was given after delivery of the baby and cord clamping, in group IM (B) oxytocin was given at the point of delivery of the anterior shoulder. Total number randomised = 300 in IM group. We have combined the 2 IV and IM groups to form a single IV versus IM comparison. None of the women in any of the groups received epidural or narcotics. Cord traction and late cord clamping were not applied (cord clamped at 1 minute unless early intervention for the infant was needed). If the placenta was not delivered after 30 minutes additional oxytocin (10 IU) was given (route not clear) and if no change manual removal of the placenta was performed under sedation. Women with blood loss > 500 mL also given additional oxytocin (10 IU) and if the uterus was atonic massage performed.
Outcomes	Serious maternal morbidity, maternal death, blood loss ≥ 600 mL, mean blood loss (estimated using a sterile calibrated drape), use of additional uterotonics, mean duration of 3rd stage, retained placenta, postpartum haematocrit and haemoglobin. Subgroup analysis by induction.
Notes	**Funding:** source not stated.

Oguz 2014 *(Continued)*

CoI: reported that there was no conflict of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reported using random number table. No other information provided. There were 4 equal sized groups.
Allocation concealment (selection bias)	Unclear risk	It was not clear how allocation was concealed or at what point women were randomised.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Staff providing care and making decisions about management were not blinded and this may have had an impact on some outcomes, although outcomes such as haemoglobin may not have been affected and interventions were not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was reported that staff measuring the blood-loss outcome were blinded to treatment group although it was not clear whether other outcomes would be affected by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	It appeared from the tables that there was no loss to follow-up. It was not clear whether there were any missing data for any outcomes.
Selective reporting (reporting bias)	High risk	Retrospective study registration (NCT01954186). Only a limited number of outcomes were reported. Important outcomes such as need for transfusion and severe PPH were not reported. It was not clear why the cut-off of 600 mL was used for PPH; this is not the usual definition and the Background section talks about PPH as blood loss > 500 or 1000 mL.
Other bias	Unclear risk	One of the groups had more women who had labour induction. Other baseline characteristics were similar.

Sangkhomkhamhang 2015

Study characteristics

Methods	RCT
Participants	**Setting:** women attending Khon Kaen Hospital, Thailand. **Dates of recruitment:** from February to June 2012. **Total randomised:** 450 women. **Inclusion criteria**: women with singleton pregnancy attending hospital for a vaginal birth. **Exclusion criteria**: women with obstetric complications or medical problems. Women with a previous history of curettage, manual removal of the placenta, cardiovascular instability or oxytocin hypersensitivity.
Interventions	**Experimental intervention**: IV 10 IU of oxytocin in 10 mL normal saline administered over 2 minute after delivery of the anterior shoulder. Number randomised = 225 women. **Control/Comparison intervention**: IM 10 IU of oxytocin after delivery of the anterior shoulder. Number randomised = 225 women.

Sangkhomkhamhang 2015 *(Continued)*

Outcomes	Incidence of PPH (not defined) within 24 hours of the birth. Mean blood loss (measured from cord clamping until complete repair of episiotomy using plastic bags and scale), prolonged 3rd stage, retained placenta for > 30 minutes, use of additional uterotonics, blood transfusion.
Notes	**Funding:** not reported. **CoI:** not stated in the published report.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Quote: "The allocation was randomly carried out by using an assignment card placed in a sealed envelope which would be picked by each sample to be assigned into 1 of the two treatment groups." Comment: description unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No attempt at blinding and women and staff would be aware of treatment allocation because of different modes of administration.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes would be recorded by staff aware of allocation. Several of the outcomes (e.g. estimated blood loss) may have been affected by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was no mention of sample attrition or missing data.
Selective reporting (reporting bias)	Low risk	Trial registration available (ACTRN12612000624886). Some of the outcomes were not fully reported, e.g. reported as no significant differences between groups.
Other bias	Low risk	Groups appeared similar at baseline and no other sources of bias were apparent.

CoI: conflict of Interest; **Hb**: haemoglobin; **HELLP**: haemolysis, elevated liver enzymes, and low platelets; **IM**: intramuscular; **IU**: international units; **IV**: intravenous; **PPH**: postpartum haemorrhage; **RCT**: randomised controlled trial

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

Study	Reason for exclusion
NCT03651882	Not eligible intervention. Oxytocin 10 IU intramyometrially plus 10 IU administered by an IV infusion over 12 hours versus carbetocin 100 mcg administered by an IV bolus injection after delivery for the prevention of PPH.
Sheldon 2011	Secondary data analysis from a non-inferiority RCT of sublingual misoprostol versus IV oxytocin for the treatment of postpartum haemorrhage (Blum 2010). All women in the trial had initially received oxytocin following the birth of the baby as part of routine management of the 3rd stage of labour. Women were randomised only after diagnosis of PPH.

IU: international units; **IV**: intravenous; **PPH**: postpartum haemorrhage; **RCT**: randomised controlled trial

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

Ashwal 2016

Methods	3-arm RCT
Participants	210 women with a term pregnancy in the 3rd stage of labour, undergoing vaginal birth in a single tertiary hospital between 2014 and 2015.
Interventions	Trial compared 3 different oxytocin regimens: 1. 10 IU IV oxytocin in 100 mL 0.9% sodium chloride over 10 minutes 2. 10 IU IM oxytocin 3. combined IV + IM regimens
Outcomes	Changes in haemoglobin and haematocrit measurements (prepartum to 24-48 hours postpartum).
Notes	This report is a brief abstract and results are reported in a graph. We have tried to contact the authors, but received no response. This study will be reassessed for inclusion in the next update.

NCT00200252

Methods	3-arm RCT (not blinded)
Participants	300 women with a singleton pregnancy of at least 32 weeks' gestation in the 3rd stage of labour, undergoing spontaneous vaginal birth in a hospital setting in Canada.
Interventions	Trial compared 3 different oxytocin regimens: 1. 5 IU IV oxytocin 2. 5 IU IM oxytocin 3. 10 IU IM oxytocin
Outcomes	Change in haematocrit, estimated blood loss, blood loss ≥ 500 mL, blood loss ≥ 1000 mL, hypotension, duration of 3rd stage of labour, blood transfusion, retained placenta, need for dilatation and curettage, hysterectomy, additional uterotonics, antibiotic use, maternal satisfaction, bleeding leading to readmission to hospital.
Notes	This study was completed in 2007, but no published results were identified. We have tried to contact trial authors but received no response. This study will be reassessed for inclusion in the next update.

NCT02319707

Methods	3-arm RCT (not blinded)
Participants	Women with a singleton pregnancy of at least 34 weeks' gestation in the 3rd stage of labour.
Interventions	Trial compared 3 different oxytocin regimens: 1. 10 IU IV oxytocin in 100 mL 0.9% sodium chloride during the 3rd stage 2. 10 IU IM oxytocin during the 3rd stage

NCT02319707 *(Continued)*	
	3. combined IV + IM regimens
Outcomes	Haemoglobin changes (prepartum to 24-48 hours postpartum), blood count changes (prepartum to 24-48 hours postpartum).
Notes	Reported start date September 2015, completion January 2017. The status of this trial is unknown. We have been unable to contact authors. We will reassess at the time of the next update.

IM: intramuscular; **IV**: intravenous; **RCT**: randomised controlled trial

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

ACTRN12617000176369	
Study name	Postpartum hemorrhage (PPH) prevention: oxytocin pharmacokinetics and maternal body mass index (BMI).
Methods	2-arm RCT (not blinded)
Participants	Women with a term singleton pregnancy in the 3rd stage of labour, undergoing either vaginal birth or caesarean delivery in a hospital setting in Australia. According to their BMI at booking, women will be classified as either normal (18.5-24.99 Kg/m^2), overweight (25-29.99 Kg/m^2), obese class I (30-34.99 Kg/m^2), obese class II, (35-39.99 Kg/m^2) or obese class III (≥ 40.00 Kg/m^2).
Interventions	Trial compared 2 different oxytocin regimens: 1. 5 IU IV oxytocin over 1-2 minutes 2. 10 IU IM oxytocin
Outcomes	Absolute bioavailability, absorption rate constant, clearance, and volume of distribution, maximum plasma concentration (Cmax), time to Cmax, area under the plasma concentration-time curve (AUC), and terminal phase half-life (t 1/2).
Starting date	01/12/2020
Contact information	Department of Obstetrics and Gynaecology, Monash University, Monash Medical Centre, Clayton, Victoria 3168. Professor Euan M Wallace euan.wallace@monash.edu
Notes	Prospectively registered on 02/02/2017. This study was last updated on 22/01/2020. Current status: not yet recruiting. This study will be re-assessed for inclusion in the next update.

NCT01608958	
Study name	IV versus IM oxytocin in the 3rd stage of labour for prevention of postpartum haemorrhage.
Methods	2-arm RCT (not blinded)
Participants	653 women in the 3rd stage of labour, undergoing a vaginal birth in a hospital setting in Vietnam, Turkey and Equador.
Interventions	Trial compared 2 different oxytocin regimens:

NCT01608958 *(Continued)*

	1. 10 IU IV oxytocin (infusion) as soon as possible after the birth 2. 10 IU IM oxytocin as soon as possible after the birth
Outcomes	Mean blood loss, blood loss ≥ 350, ≥ 500, or ≥ 1000 mL, change in haemoglobin measurements, duration of 3rd stage, additional uterotonics, side effects.
Starting date	Started 05/2012. The study has been completed.
Contact information	Trial authors were contacted and responded that the trial is completed, but results are not yet published.
Notes	This study will be reassessed for inclusion in the next update.

PACTR201902721929705

Study name	A double-blind randomised trial on comparison of intravenous and intramuscular oxytocin for preventing atonic primary postpartum haemorrhage in 3rd stage of labour.
Methods	2-arm RCT (double-blind)
Participants	Women with a term singleton pregnancy in the 3rd stage of labour, undergoing vaginal birth in a hospital setting in Nigeria.
Interventions	Trial compared 3 different oxytocin regimens: 1. 10 IU IV oxytocin over 2 minutes 2. 10 IU IM oxytocin
Outcomes	Mean blood loss, additional uterotonics, blood transfusion, additional surgical intervention, anaemia nausea, vomiting, shivering, hypotension.
Starting date	Started 19/02/2019.
Contact information	49 Nnewi Onitsha Road, 435001, Nnewi, Nigeria Principal investigator: Emmanuel Okaforcha emmanuelokaforwhite@gmail.com
Notes	The status of this trial was last updated on 11/6/2019 (recruiting). This study will be reassessed for inclusion in the next update.

IM: intramuscular; **IU**: international units; **IV**: intravenous; **RCT**: randomised controlled trial

DATA AND ANALYSES

Comparison 1. IV versus IM oxytocin

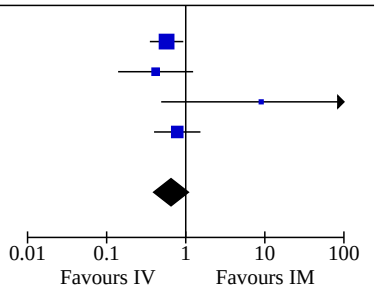
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Severe PPH ≥ 1000 mL	4	6681	Risk Ratio (IV, Random, 95% CI)	0.65 [0.39, 1.08]
1.2 Serious maternal morbidity	4	7028	Risk Ratio (IV, Random, 95% CI)	0.47 [0.22, 1.00]
1.3 Maternal death	4	7028	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.4 PPH ≥ 500 mL	6	7731	Risk Ratio (IV, Random, 95% CI)	0.78 [0.66, 0.92]
1.5 Mean blood loss mL	6		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.6 Use of additional uterotonics	6	7327	Risk Ratio (IV, Random, 95% CI)	0.78 [0.49, 1.25]
1.7 Blood transfusion	4	6684	Risk Ratio (IV, Random, 95% CI)	0.44 [0.26, 0.77]
1.8 Third stage duration > 30 minutes	1	450	Risk Ratio (IV, Random, 95% CI)	0.82 [0.35, 1.94]
1.9 Mean duration of 3rd stage (minutes)	3		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.10 Retained placenta or manual removal of placenta	5	6292	Risk Ratio (IV, Random, 95% CI)	0.73 [0.52, 1.03]
1.11 Maternal postpartum anaemia	3	6188	Risk Ratio (IV, Random, 95% CI)	0.99 [0.84, 1.16]
1.12 Mean postpartum Hb levels (g/L)	2	856	Mean Difference (IV, Random, 95% CI)	0.00 [-1.76, 1.77]
1.13 Any adverse effect reported	1	1035	Risk Ratio (IV, Random, 95% CI)	0.78 [0.45, 1.36]
1.14 Nausea	2	1515	Risk Ratio (IV, Random, 95% CI)	1.00 [0.06, 15.98]
1.15 Vomiting	2	1515	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.16 Diarrhoea	1	480	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.17 Fever	1	480	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.18 Shivering	2	1515	Risk Ratio (IV, Random, 95% CI)	0.40 [0.08, 2.06]
1.19 Headache	2	1515	Risk Ratio (IV, Random, 95% CI)	0.75 [0.17, 3.34]
1.20 Hypotension	4	6468	Risk Ratio (IV, Random, 95% CI)	1.01 [0.88, 1.15]
1.21 Tachycardia	2	1513	Risk Ratio (IV, Random, 95% CI)	0.89 [0.68, 1.16]
1.22 Maternal dissatisfaction with intervention	0	0	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.23 Providers' dissatisfaction with intervention	0	0	Risk Ratio (IV, Random, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.24 Apgar score less than 7 at 5 minutes	0	0	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.25 Neonatal jaundice	0	0	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.26 Admission to SCBU	0	0	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.27 Not breastfeeding at hospital discharge	1	1035	Risk Ratio (IV, Random, 95% CI)	0.96 [0.84, 1.10]

Analysis 1.1. Comparison 1: IV versus IM oxytocin, Outcome 1: Severe PPH ≥ 1000 mL

Study or Subgroup	IV oxytocin Events	IV oxytocin Total	IM oxytocin Events	IM oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Adnan 2018	24	517	42	518	46.8%	0.57 [0.35 , 0.93]
Charles 2019	5	2809	9	2104	17.0%	0.42 [0.14 , 1.24]
Dagdeviren 2016	4	128	0	128	2.9%	9.00 [0.49 , 165.46]
Durocher 2019	14	238	18	239	33.4%	0.78 [0.40 , 1.53]
Total (95% CI)		**3692**		**2989**	**100.0%**	**0.65 [0.39 , 1.08]**
Total events:	47		69			

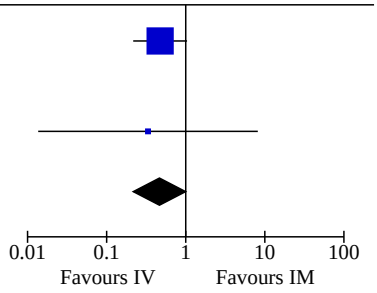
Heterogeneity: Tau² = 0.08; Chi² = 4.30, df = 3 (P = 0.23); I² = 30%
Test for overall effect: Z = 1.66 (P = 0.10)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: IV versus IM oxytocin, Outcome 2: Serious maternal morbidity

Study or Subgroup	Favours IV Events	Favours IV Total	IM oxytocin Events	IM oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Adnan 2018 (1)	9	517	19	518	94.3%	0.47 [0.22 , 1.04]
Charles 2019	0	2809	0	2104		Not estimable
Durocher 2019	0	239	0	241		Not estimable
Oguz 2014 (2)	0	300	1	300	5.7%	0.33 [0.01 , 8.15]
Total (95% CI)		**3865**		**3163**	**100.0%**	**0.47 [0.22 , 1.00]**
Total events:	9		20			

Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.97 (P = 0.05)
Test for subgroup differences: Not applicable



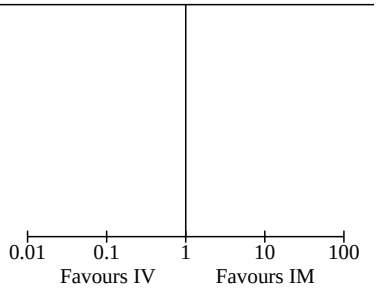
Footnotes

(1) Hight Dependency Unit (HDU) admissions.
(2) Uvular oedema.

Analysis 1.3. Comparison 1: IV versus IM oxytocin, Outcome 3: Maternal death

Study or Subgroup	IV oxytocin Events	IV oxytocin Total	IM oxytocin Events	IM oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Adnan 2018	0	517	0	518		Not estimable
Charles 2019	0	2809	0	2104		Not estimable
Durocher 2019	0	239	0	241		Not estimable
Oguz 2014	0	300	0	300		Not estimable
Total (95% CI)		**3865**		**3163**		**Not estimable**
Total events:	0		0			

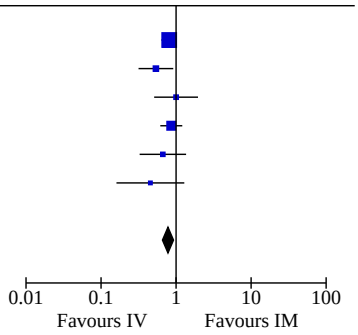
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: IV versus IM oxytocin, Outcome 4: PPH ≥ 500 mL

Study or Subgroup	IV oxytocin Events	IV oxytocin Total	IM oxytocin Events	IM oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Adnan 2018	97	517	120	518	50.3%	0.81 [0.64 , 1.03]
Charles 2019	23	2809	32	2104	10.1%	0.54 [0.32 , 0.92]
Dagdeviren 2016	15	128	15	128	6.3%	1.00 [0.51 , 1.96]
Durocher 2019	49	238	57	239	25.1%	0.86 [0.62 , 1.21]
Oguz 2014 (1)	12	300	18	300	5.6%	0.67 [0.33 , 1.36]
Sangkhomkhamhang 2015 (2)	5	225	11	225	2.6%	0.45 [0.16 , 1.29]
Total (95% CI)		**4217**		**3514**	**100.0%**	**0.78 [0.66 , 0.92]**
Total events:	201		253			

Heterogeneity: Tau² = 0.00; Chi² = 4.05, df = 5 (P = 0.54); I² = 0%
Test for overall effect: Z = 2.89 (P = 0.004)
Test for subgroup differences: Not applicable



Footnotes

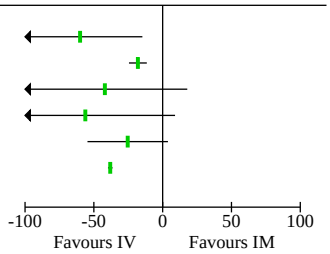
(1) Reporte blood loss >600 mL.
(2) Measured from cord clamp till repair of the episiotomy. PPH not clearly defined by study authors.

Analysis 1.5. Comparison 1: IV versus IM oxytocin, Outcome 5: Mean blood loss mL

Study or Subgroup	IV oxytocin Mean	IV oxytocin SD	IV oxytocin Total	IM oxytocin Mean	IM oxytocin SD	IM oxytocin Total	Mean Difference IV, Random, 95% CI
Adnan 2018	385	326	517	445	412	518	-60.00 [-105.26 , -14.74]
Charles 2019	186	111.4	2809	204	117	2104	-18.00 [-24.48 , -11.52]
Durocher 2019	364	323	238	406	344	239	-42.00 [-101.88 , 17.88]
Neri-Mejia 2016	97.8	96	21	154	121.2	22	-56.20 [-121.40 , 9.00]
Oguz 2014	239.5	182.5	300	264.9	182.8	300	-25.40 [-54.63 , 3.83]
Sangkhomkhamhang 2015 (1)	116.3	6.9	225	154.4	10.5	225	-38.10 [-39.74 , -36.46]

Footnotes

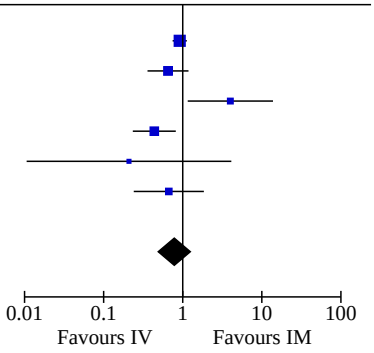
(1) Measured from cord clamp till repair of the episiotomy.



Analysis 1.6. Comparison 1: IV versus IM oxytocin, Outcome 6: Use of additional uterotonics

Study or Subgroup	IV oxytocin Events	IV oxytocin Total	IM oxytocin Events	IM oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Adnan 2018	128	517	140	518	31.9%	0.92 [0.75 , 1.13]
Charles 2019	20	2809	23	2104	21.8%	0.65 [0.36 , 1.18]
Dagdeviren 2016	12	128	3	128	10.0%	4.00 [1.16 , 13.84]
Durocher 2019	13	239	30	241	21.1%	0.44 [0.23 , 0.82]
Neri-Mejia 2016	0	21	2	22	2.3%	0.21 [0.01 , 4.11]
Oguz 2014	6	300	9	300	12.9%	0.67 [0.24 , 1.85]
Total (95% CI)		**4014**		**3313**	**100.0%**	**0.78 [0.49 , 1.25]**
Total events:	179		207			

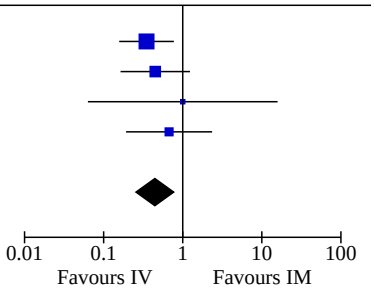
Heterogeneity: Tau² = 0.17; Chi² = 12.66, df = 5 (P = 0.03); I² = 61%
Test for overall effect: Z = 1.04 (P = 0.30)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: IV versus IM oxytocin, Outcome 7: Blood transfusion

Study or Subgroup	IV oxytocin Events	IV oxytocin Total	IM oxytocin Events	IM oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Adnan 2018	8	517	23	518	47.5%	0.35 [0.16 , 0.77]
Charles 2019	6	2809	10	2104	29.4%	0.45 [0.16 , 1.23]
Dagdeviren 2016	1	128	1	128	3.9%	1.00 [0.06 , 15.82]
Durocher 2019	4	239	6	241	19.1%	0.67 [0.19 , 2.35]
Total (95% CI)		**3693**		**2991**	**100.0%**	**0.44 [0.26 , 0.77]**
Total events:	19		40			

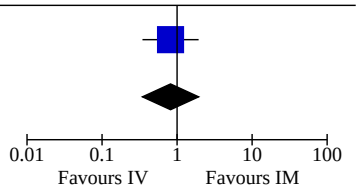
Heterogeneity: Tau² = 0.00; Chi² = 1.11, df = 3 (P = 0.77); I² = 0%
Test for overall effect: Z = 2.90 (P = 0.004)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: IV versus IM oxytocin, Outcome 8: Third stage duration > 30 minutes

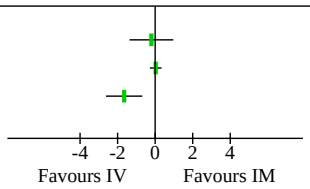
Study or Subgroup	IV oxytocin Events	IV oxytocin Total	IM oxytocin Events	IM oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Sangkhomkhamhang 2015	9	225	11	225	100.0%	0.82 [0.35 , 1.94]
Total (95% CI)		**225**		**225**	**100.0%**	**0.82 [0.35 , 1.94]**
Total events:	9		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.65)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: IV versus IM oxytocin, Outcome 9: Mean duration of 3rd stage (minutes)

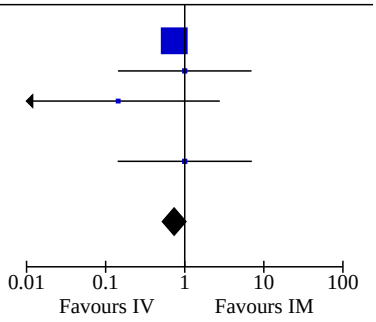
Study or Subgroup	IV oxytocin Mean	SD	Total	IM oxytocin Mean	SD	Total	Mean Difference IV, Random, 95% CI
Durocher 2019	6.4	5.7	239	6.6	7.2	239	-0.20 [-1.36 , 0.96]
Neri-Mejia 2016	1.55	0.58	21	1.52	0.45	22	0.03 [-0.28 , 0.34]
Oguz 2014	10.75	6	300	12.4	6.1	300	-1.65 [-2.62 , -0.68]



Analysis 1.10. Comparison 1: IV versus IM oxytocin, Outcome 10: Retained placenta or manual removal of placenta

Study or Subgroup	IV oxytocin Events	Total	IM oxytocin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Charles 2019	59	2809	60	2104	92.5%	0.74 [0.52 , 1.05]
Dagdeviren 2016	2	128	2	128	3.1%	1.00 [0.14 , 6.99]
Durocher 2019	0	239	3	241	1.3%	0.14 [0.01 , 2.77]
Neri-Mejia 2016	0	21	0	22		Not estimable
Oguz 2014	2	300	2	300	3.1%	1.00 [0.14 , 7.05]
Total (95% CI)		**3497**		**2795**	**100.0%**	**0.73 [0.52 , 1.03]**
Total events:	63		67			

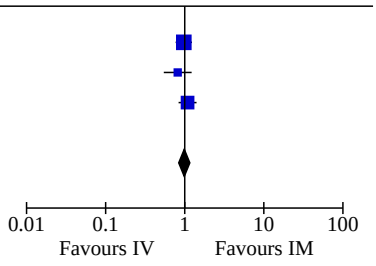
Heterogeneity: Tau² = 0.00; Chi² = 1.36, df = 3 (P = 0.72); I² = 0%
Test for overall effect: Z = 1.77 (P = 0.08)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: IV versus IM oxytocin, Outcome 11: Maternal postpartum anaemia

Study or Subgroup	IV oxytocin Events	Total	IM oxytocin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Adnan 2018 (1)	100	405	104	410	46.0%	0.97 [0.77 , 1.23]
Charles 2019 (2)	48	2803	44	2094	15.8%	0.81 [0.54 , 1.22]
Durocher 2019 (3)	79	236	74	240	38.1%	1.09 [0.84 , 1.41]
Total (95% CI)		**3444**		**2744**	**100.0%**	**0.99 [0.84 , 1.16]**
Total events:	227		222			

Heterogeneity: Tau² = 0.00; Chi² = 1.38, df = 2 (P = 0.50); I² = 0%
Test for overall effect: Z = 0.16 (P = 0.87)
Test for subgroup differences: Not applicable



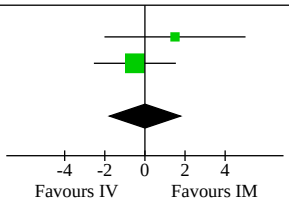
Footnotes

(1) Drop in Hb levels by #20% 24 hours after delivery. Balanced attrition bias >10%.
(2) Drop in Hb levels by #2g/dL 24 hours after delivery, excluding women who received a blood transfusion.
(3) Drop in Hb levels by #2g/dL 24-48 hours after delivery or given a blood transfusion.

Analysis 1.12. Comparison 1: IV versus IM oxytocin, Outcome 12: Mean postpartum Hb levels (g/L)

Study or Subgroup	IV oxytocin Mean	SD	Total	IM oxytocin Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Dagdeviren 2016	105	14.3	128	103.5	14.4	128	25.2%	1.50 [-2.02 , 5.02]
Oguz 2014	109	12.5	300	109.5	13.03	300	74.8%	-0.50 [-2.54 , 1.54]
Total (95% CI)			**428**			**428**	**100.0%**	**0.00 [-1.76 , 1.77]**

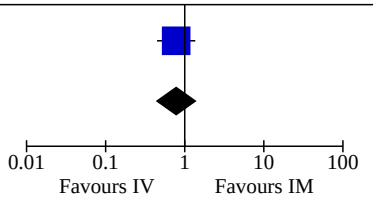
Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 0.01 (P = 1.00)
Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1: IV versus IM oxytocin, Outcome 13: Any adverse effect reported

Study or Subgroup	IV oxytocin Events	Total	IM oxytocin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Adnan 2018	21	517	27	518	100.0%	0.78 [0.45 , 1.36]
Total (95% CI)		**517**		**518**	**100.0%**	**0.78 [0.45 , 1.36]**
Total events:	21		27			

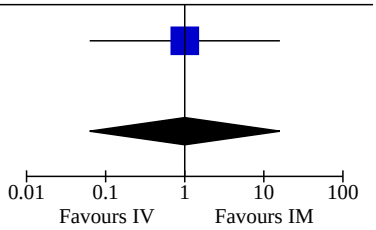
Heterogeneity: Not applicable
Test for overall effect: Z = 0.88 (P = 0.38)
Test for subgroup differences: Not applicable



Analysis 1.14. Comparison 1: IV versus IM oxytocin, Outcome 14: Nausea

Study or Subgroup	IV oxytocin Events	Total	IM oxytocin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Adnan 2018	1	517	1	518	100.0%	1.00 [0.06 , 15.98]
Durocher 2019	0	239	0	241		Not estimable
Total (95% CI)		**756**		**759**	**100.0%**	**1.00 [0.06 , 15.98]**
Total events:	1		1			

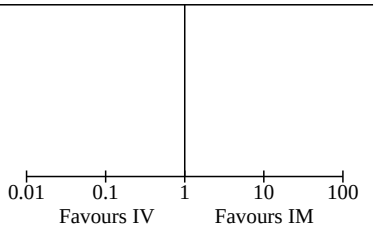
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



Analysis 1.15. Comparison 1: IV versus IM oxytocin, Outcome 15: Vomiting

Study or Subgroup	IV oxytocin Events	Total	IM oxytocin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Adnan 2018	0	517	0	518		Not estimable
Durocher 2019	0	239	0	241		Not estimable
Total (95% CI)		**756**		**759**		**Not estimable**
Total events:	0		0			

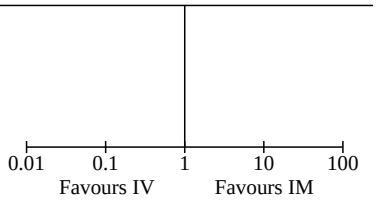
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 1.16. Comparison 1: IV versus IM oxytocin, Outcome 16: Diarrhoea

Study or Subgroup	IV oxytocin Events	IV oxytocin Total	IM oxytocin Events	IM oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Durocher 2019	0	239	0	241		Not estimable
Total (95% CI)		**239**		**241**		**Not estimable**
Total events:	0		0			

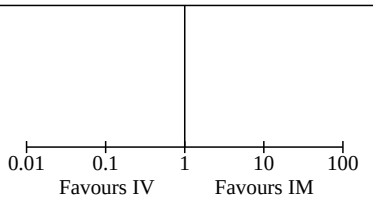
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 1.17. Comparison 1: IV versus IM oxytocin, Outcome 17: Fever

Study or Subgroup	IV oxytocin Events	IV oxytocin Total	IM oxytocin Events	IM oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Durocher 2019	0	239	0	241		Not estimable
Total (95% CI)		**239**		**241**		**Not estimable**
Total events:	0		0			

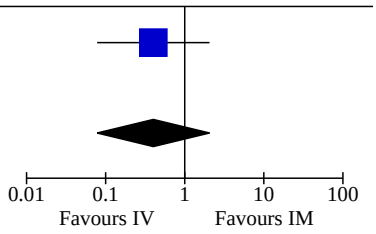
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 1.18. Comparison 1: IV versus IM oxytocin, Outcome 18: Shivering

Study or Subgroup	IV oxytocin Events	IV oxytocin Total	IM oxytocin Events	IM oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Adnan 2018	2	517	5	518	100.0%	0.40 [0.08 , 2.06]
Durocher 2019	0	239	0	241		Not estimable
Total (95% CI)		**756**		**759**	**100.0%**	**0.40 [0.08 , 2.06]**
Total events:	2		5			

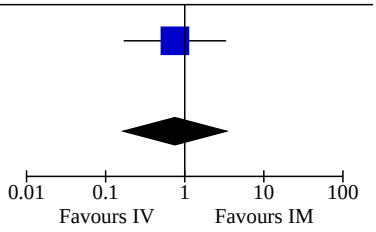
Heterogeneity: Not applicable
Test for overall effect: Z = 1.10 (P = 0.27)
Test for subgroup differences: Not applicable



Analysis 1.19. Comparison 1: IV versus IM oxytocin, Outcome 19: Headache

Study or Subgroup	IV oxytocin Events	IV oxytocin Total	IM oxytocin Events	IM oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Adnan 2018	3	517	4	518	100.0%	0.75 [0.17 , 3.34]
Durocher 2019	0	239	0	241		Not estimable
Total (95% CI)		**756**		**759**	**100.0%**	**0.75 [0.17 , 3.34]**
Total events:	3		4			

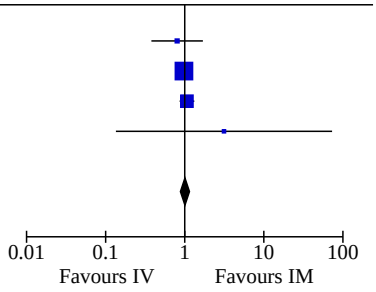
Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.71)
Test for subgroup differences: Not applicable



Analysis 1.20. Comparison 1: IV versus IM oxytocin, Outcome 20: Hypotension

Study or Subgroup	IV oxytocin Events	IV oxytocin Total	IM oxytocin Events	IM oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Adnan 2018 (1)	12	517	15	518	3.1%	0.80 [0.38 , 1.70]
Charles 2019 (2)	274	2809	210	2104	59.0%	0.98 [0.82 , 1.16]
Durocher 2019 (3)	102	238	96	239	37.8%	1.07 [0.86 , 1.32]
Neri-Mejia 2016	1	21	0	22	0.2%	3.14 [0.13 , 72.96]
Total (95% CI)		**3585**		**2883**	**100.0%**	**1.01 [0.88 , 1.15]**
Total events:	389		321			

Heterogeneity: Tau² = 0.00; Chi² = 1.26, df = 3 (P = 0.74); I² = 0%
Test for overall effect: Z = 0.09 (P = 0.93)
Test for subgroup differences: Not applicable

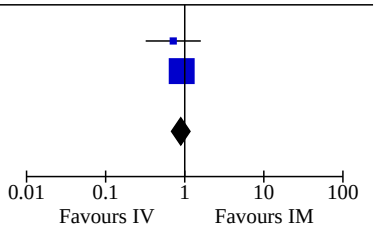


Footnotes
(1) BP >30% lower than predelivery measurements, or use of ephedrine, or both.
(2) Diastolic BP #60 mmHg.
(3) Either Systolic BP #90 mmHg or Diastolic BP #60 mmHg.

Analysis 1.21. Comparison 1: IV versus IM oxytocin, Outcome 21: Tachycardia

Study or Subgroup	IV oxytocin Events	IV oxytocin Total	IM oxytocin Events	IM oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Adnan 2018	10	517	14	518	11.2%	0.72 [0.32 , 1.60]
Durocher 2019	65	239	71	239	88.8%	0.92 [0.69 , 1.22]
Total (95% CI)		**756**		**757**	**100.0%**	**0.89 [0.68 , 1.16]**
Total events:	75		85			

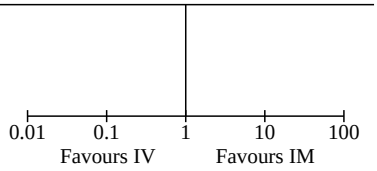
Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 0.85 (P = 0.40)
Test for subgroup differences: Not applicable



Analysis 1.22. Comparison 1: IV versus IM oxytocin, Outcome 22: Maternal dissatisfaction with intervention

Study or Subgroup	IV oxytocin Events	IV oxytocin Total	IM oxytocin Events	IM oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			

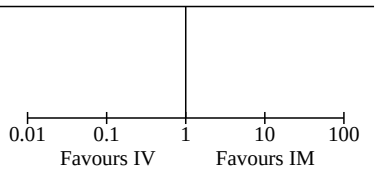
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 1.23. Comparison 1: IV versus IM oxytocin, Outcome 23: Providers' dissatisfaction with intervention

Study or Subgroup	IV oxytocin Events	IV oxytocin Total	IM oxytocin Events	IM oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			

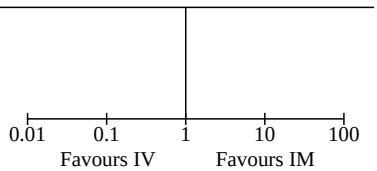
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 1.24. Comparison 1: IV versus IM oxytocin, Outcome 24: Apgar score less than 7 at 5 minutes

Study or Subgroup	IV oxytocin Events	IV oxytocin Total	IM oxytocin Events	IM oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			

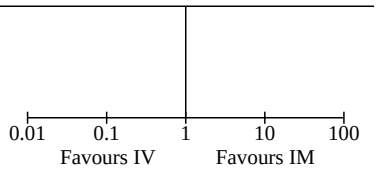
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 1.25. Comparison 1: IV versus IM oxytocin, Outcome 25: Neonatal jaundice

Study or Subgroup	IV oxytocin Events	IV oxytocin Total	IM oxytocin Events	IM oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			

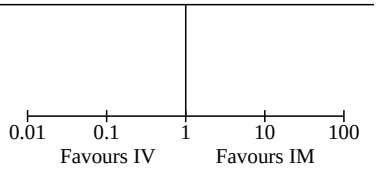
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 1.26. Comparison 1: IV versus IM oxytocin, Outcome 26: Admission to SCBU

Study or Subgroup	IV oxytocin Events	IV oxytocin Total	IM oxytocin Events	IM oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			

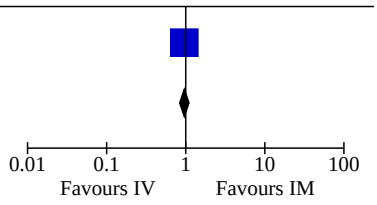
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 1.27. Comparison 1: IV versus IM oxytocin, Outcome 27: Not breastfeeding at hospital discharge

Study or Subgroup	IV oxytocin Events	IV oxytocin Total	IM oxytocin Events	IM oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Adnan 2018	228	517	238	518	100.0%	0.96 [0.84 , 1.10]
Total (95% CI)		**517**		**518**	**100.0%**	**0.96 [0.84 , 1.10]**
Total events:	228		238			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.60 (P = 0.55)
Test for subgroup differences: Not applicable

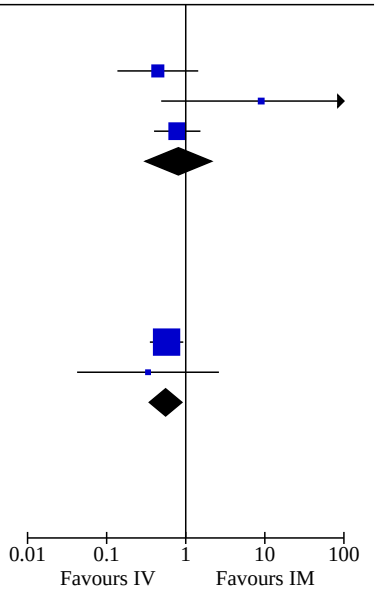


Comparison 2. IV versus IM oxytocin (by type of IV administration)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.1 PPH ≥ 1000 mL	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.1.1 IV infusion versus IM	3	4945	Risk Ratio (IV, Random, 95% CI)	0.81 [0.31, 2.12]
2.1.2 IV bolus versus IM	2	3840	Risk Ratio (IV, Random, 95% CI)	0.56 [0.35, 0.89]
2.2 Serious maternal morbidity	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.2.1 IV infusion versus IM	2	4692	Risk Ratio (IV, Random, 95% CI)	Not estimable
2.2.2 IV bolus versus IM	3	4440	Risk Ratio (IV, Random, 95% CI)	0.47 [0.22, 1.00]

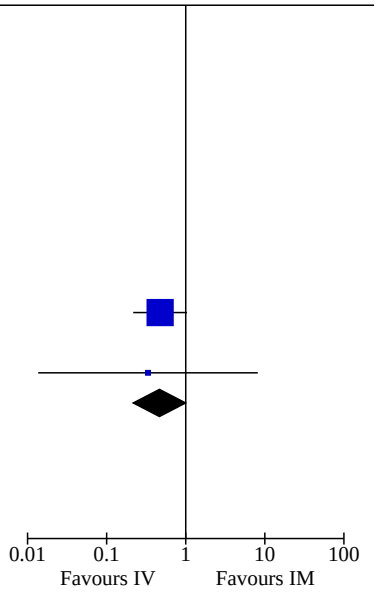
Analysis 2.1. Comparison 2: IV versus IM oxytocin (by type of IV administration), Outcome 1: PPH ≥ 1000 mL

Study or Subgroup	IV oxytocin Events	IV oxytocin Total	IM oxytocin Events	IM oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
2.1.1 IV infusion versus IM						
Charles 2019	4	2108	9	2104	35.5%	0.44 [0.14 , 1.44]
Dagdeviren 2016	4	128	0	128	9.6%	9.00 [0.49 , 165.46]
Durocher 2019	14	238	18	239	54.9%	0.78 [0.40 , 1.53]
Subtotal (95% CI)		**2474**		**2471**	**100.0%**	**0.81 [0.31 , 2.12]**
Total events:	22		27			
Heterogeneity: Tau² = 0.32; Chi² = 3.58, df = 2 (P = 0.17); I² = 44%						
Test for overall effect: Z = 0.43 (P = 0.66)						
2.1.2 IV bolus versus IM						
Adnan 2018	24	517	42	518	94.7%	0.57 [0.35 , 0.93]
Charles 2019	1	701	9	2104	5.3%	0.33 [0.04 , 2.63]
Subtotal (95% CI)		**1218**		**2622**	**100.0%**	**0.56 [0.35 , 0.89]**
Total events:	25		51			
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.62); I² = 0%						
Test for overall effect: Z = 2.43 (P = 0.02)						
Test for subgroup differences: Chi² = 0.46, df = 1 (P = 0.50), I² = 0%						



Analysis 2.2. Comparison 2: IV versus IM oxytocin (by type of IV administration), Outcome 2: Serious maternal morbidity

Study or Subgroup	IV oxytocin Events	IV oxytocin Total	IM oxytocin Events	IM oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
2.2.1 IV infusion versus IM						
Charles 2019	0	2108	0	2104		Not estimable
Durocher 2019	0	239	0	241		Not estimable
Subtotal (95% CI)		**2347**		**2345**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.2.2 IV bolus versus IM						
Adnan 2018 (1)	9	517	19	518	94.3%	0.47 [0.22 , 1.04]
Charles 2019	0	701	0	2104		Not estimable
Oguz 2014 (2)	0	300	1	300	5.7%	0.33 [0.01 , 8.15]
Subtotal (95% CI)		**1518**		**2922**	**100.0%**	**0.47 [0.22 , 1.00]**
Total events:	9		20			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.83); I² = 0%						
Test for overall effect: Z = 1.97 (P = 0.05)						
Test for subgroup differences: Not applicable						



Footnotes

(1) Hight Dependency Unit (HDU) admissions.

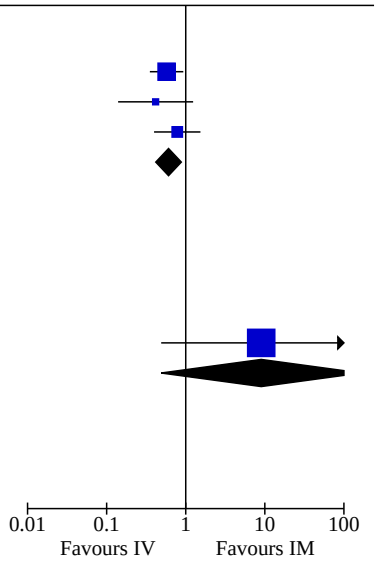
(2) Uvular oedema.

Comparison 3. IV versus IM oxytocin (by type of further management

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Severe PPH ≥ 1000 mL	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.1.1 IV versus IM with AMTSL	3	6425	Risk Ratio (IV, Random, 95% CI)	0.61 [0.42, 0.88]
3.1.2 IV versus IM without AMTSL	1	256	Risk Ratio (IV, Random, 95% CI)	9.00 [0.49, 165.46]
3.2 Serious maternal morbidity	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.2.1 IV versus IM with AMTSL	3	6428	Risk Ratio (IV, Random, 95% CI)	0.47 [0.22, 1.04]
3.2.2 IV versus IM without AMTSL	1	600	Risk Ratio (IV, Random, 95% CI)	0.33 [0.01, 8.15]

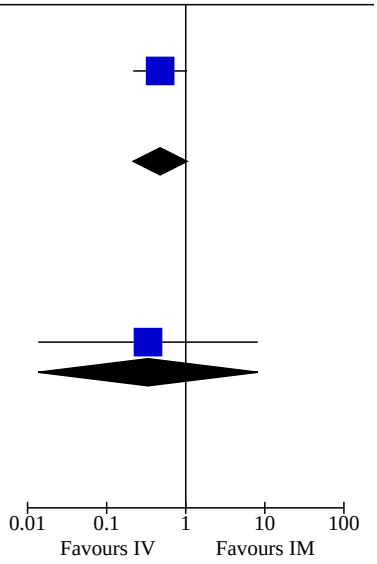
Analysis 3.1. Comparison 3: IV versus IM oxytocin (by type of further management, Outcome 1: Severe PPH ≥ 1000 mL

Study or Subgroup	IV oxytocin Events	IV oxytocin Total	IM oxytocin Events	IM oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
3.1.1 IV versus IM with AMTSL						
Adnan 2018	24	517	42	518	58.2%	0.57 [0.35 , 0.93]
Charles 2019	5	2809	9	2104	11.6%	0.42 [0.14 , 1.24]
Durocher 2019	14	238	18	239	30.2%	0.78 [0.40 , 1.53]
Subtotal (95% CI)		**3564**		**2861**	**100.0%**	**0.61 [0.42 , 0.88]**
Total events:	43		69			
Heterogeneity: Tau² = 0.00; Chi² = 1.05, df = 2 (P = 0.59); I² = 0%						
Test for overall effect: Z = 2.64 (P = 0.008)						
3.1.2 IV versus IM without AMTSL						
Dagdeviren 2016	4	128	0	128	100.0%	9.00 [0.49 , 165.46]
Subtotal (95% CI)		**128**		**128**	**100.0%**	**9.00 [0.49 , 165.46]**
Total events:	4		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.48 (P = 0.14)						
Test for subgroup differences: Chi² = 3.25, df = 1 (P = 0.07), I² = 69.2%						



Analysis 3.2. Comparison 3: IV versus IM oxytocin (by type of further management, Outcome 2: Serious maternal morbidity

Study or Subgroup	IV oxytocin Events	IV oxytocin Total	IM oxytocin Events	IM oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
3.2.1 IV versus IM with AMTSL						
Adnan 2018 (1)	9	517	19	518	100.0%	0.47 [0.22 , 1.04]
Charles 2019	0	2809	0	2104		Not estimable
Durocher 2019	0	239	0	241		Not estimable
Subtotal (95% CI)		**3565**		**2863**	**100.0%**	**0.47 [0.22 , 1.04]**
Total events:	9		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.86 (P = 0.06)						
3.2.2 IV versus IM without AMTSL						
Oguz 2014 (2)	0	300	1	300	100.0%	0.33 [0.01 , 8.15]
Subtotal (95% CI)		**300**		**300**	**100.0%**	**0.33 [0.01 , 8.15]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.83), I² = 0%						



Footnotes

(1) Hight Dependency Unit (HDU) admissions.

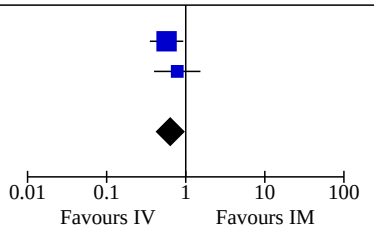
(2) Uvular oedema.

Comparison 4. IV versus IM oxytocin (sensitivity analysis)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Severe PPH ≥ 1000 mL	2	1512	Risk Ratio (IV, Random, 95% CI)	0.64 [0.43, 0.94]
4.2 Serious maternal morbidity	2	1515	Risk Ratio (IV, Random, 95% CI)	0.47 [0.22, 1.04]

Analysis 4.1. Comparison 4: IV versus IM oxytocin (sensitivity analysis), Outcome 1: Severe PPH ≥ 1000 mL

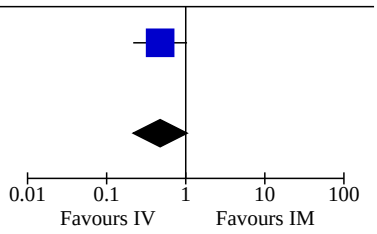
Study or Subgroup	IV oxytocin Events	IV oxytocin Total	IM oxytocin Events	IM oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Adnan 2018	24	517	42	518	65.8%	0.57 [0.35 , 0.93]
Durocher 2019	14	238	18	239	34.2%	0.78 [0.40 , 1.53]
Total (95% CI)		**755**		**757**	**100.0%**	**0.64 [0.43 , 0.94]**
Total events:	38		60			
Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 1 (P = 0.46); I² = 0%						
Test for overall effect: Z = 2.24 (P = 0.02)						
Test for subgroup differences: Not applicable						



Analysis 4.2. Comparison 4: IV versus IM oxytocin (sensitivity analysis), Outcome 2: Serious maternal morbidity

Study or Subgroup	IV oxytocin Events	IV oxytocin Total	IM oxytocin Events	IM oxytocin Total	Weight	Risk Ratio IV, Random, 95% CI
Adnan 2018 (1)	9	517	19	518	100.0%	0.47 [0.22 , 1.04]
Durocher 2019	0	239	0	241		Not estimable
Total (95% CI)		**756**		**759**	**100.0%**	**0.47 [0.22 , 1.04]**
Total events:	9		19			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.86 (P = 0.06)
Test for subgroup differences: Not applicable



Footnotes
(1) Hight Dependency Unit (HDU) admissions.

APPENDICES

Appendix 1. Search terms for ClinicalTrials.gov and ICTRP

ICTRP

intramuscular AND oxytocin AND labour

intramuscular AND oxytocin AND labor

IM AND oxytocin AND labour

IM AND oxytocin AND labor

oxytocin AND route AND labor

oxytocin AND route AND labour

ClinicalTrials.gov

Advanced search

Condition = labour OR labor

Intervention = oxytocin

Other terms = IM OR intramuscular

WHAT'S NEW

Date	Event	Description
19 December 2019	New citation required and conclusions have changed	We have included four new trials in this update. We have a total of seven trials, involving 7817 women. Two trials were excluded, three are ongoing, and three are awaiting classification. We have changed the scope of the review (from IM versus IV to IV versus IM); updated the analysis methods (from fixed effects to random effects); conducted subgroup and sensitivity analyses; revised the list of outcomes of interest, and updated the outcomes reported in the SoF table.
19 December 2019	New search has been performed	Search updated and 17 study reports assessed.

HISTORY

Protocol first published: Issue 9, 2011
Review first published: Issue 2, 2012

Date	Event	Description
13 September 2017	New search has been performed	Search updated and three studies identified for inclusion. In addition, we identified seven ongoing studies.
13 September 2017	New citation required and conclusions have changed	No studies were included in the previous version of the review. In this update we have included three studies examining intramuscular versus intravenous oxytocin.

CONTRIBUTIONS OF AUTHORS

OT Oladapo prepared the previous versions of the review and has overall responsibility for maintaining the review. For this update, A Papadopoulou and ID Gallos assessed studies for eligibility, extracted data and conducted quality assessment of included studies. A Papadopoulou and ID Gallos revised the texts of the review, the data analysis, and the GRADE assessment. OT Oladapo, BO Okusanya and E Abalos revised the final draft of the review update.

DECLARATIONS OF INTEREST

OT Oladapo: the first version of this review was performed under a contractual Agreement for Performance of Work (APW) between WHO and the contact author. No funding was allocated for the preparation of this update. However, the contact author is currently a paid staff member of the WHO.

BO Okusanya: none known.

E Abalos: none known.

ID Gallos: none known.

A Papadopoulou: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- World Health Organization (WHO) and the UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Switzerland

  This review is supported by funding to Cochrane Pregnancy and Childbirth (University of Liverpool).

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the 2018 update, we added an additional search of ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform (ICTRP). We incorporated a 'Summary of findings' table and assessment of evidence certainty using the GRADE approach. We did not pre-specify 'mean blood loss (mL)' as an outcome in the original protocol.

In the current update we have decided to revise the scope of the review. In previous versions of the review, we had treated intramuscular oxytocin administration as the intervention and intravenous oxytocin administration as the comparator to determine comparative effects. However, in the current version, we have treated intravenous oxytocin administration as the intervention and intramuscular oxytocin intervention as the comparator. This change was necessitated by the widespread use of intramuscular route for oxytocin administration which makes it more ideal as the 'standard'/'usual care'/control arm of this comparison. Additionally, we have revised the list of outcomes of interest, and we have added the following: mean third stage duration (minutes), mean postpartum haemoglobin levels (g/L), nausea, vomiting, diarrhoea, fever, shivering, headache, hypotension, tachycardia.

INDEX TERMS

Medical Subject Headings (MeSH)

Blood Transfusion [statistics & numerical data]; Injections, Intramuscular; Injections, Intravenous; *Labor Stage, Third; Oxytocics [*administration & dosage]; Oxytocin [*administration & dosage]; Postpartum Hemorrhage [epidemiology] [*prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy